The New England
Journal of Medicine

Copyright, 1952, by the Massachusetts Medical Society

Volume 246 FEBRUARY 14, 1952 Number 7

THE SURGERY OF ADVANCED PELVIC CANCER IN WOMEN*

HOWARD ULFELDER, M.D.,† AND JOE V. MEIGS, M.D.‡

BOSTON

IT has been established that removal of all the pelvic viscera can be accomplished with a mortality of 25 per cent or less and that the resultant physiologic readjustments permit a comfortable and active life.[1] The ultimate appraisal will be made in terms of patients who survive for years in good health and without disease. In the interim, however, lessons will be learned and modifications will be introduced if groups of such patients are carefully evaluated from time to time. This paper reports the facts and discusses the conclusions reached from the study of a series of 46 patients on the services of Dr. Joe V. Meigs. All ward and private cases are included and the operations were performed by Dr. Meigs or the members of his staff. Patients operated on by Dr. L. Parsons are not surveyed and have been reported separately by him.[2]

Cancer was the primary disease in all cases. Block resection of the tumor with the pelvic lymphatics and lymph nodes was done if a cure seemed possible, but whenever this goal has been compatible with preservation of the intestine or the urinary tract a less than total extirpation was performed.

TABLE 1. *Data on 8 Patients in Whom the Bowel Was Resected and the Urinary Tract Spared.*

SERIES NUMBER	DIAGNOSIS	COMPLICATIONS	NO. OF DAYS IN HOSPITAL AFTER OPERATION	SUBSEQUENT COURSE
1	Cancer of rectum into vagina	Slow to void	55	Patient still in good health 3 7/12 years postoperatively.
2	Recurrent ovarian cancer into sigmoid	0	19	Recurred in posterior wound and peritoneum; patient died in 2 years.
3	Cancer of ischiorectal fossa from Bartholin's gland (postradiation)	Deep phlebitis	18	Recurred; cordotomy at 2 years.
4	Ovarian cancer recurrent into sigmoid	Dehiscence	20	Recurred in abdominal wall; patient died in 1½ years.
5	Cancer of posterior vagina	0	30	Patient still in good health 1½ years postoperatively
6	Rectovaginal fistula and tumor; cancer of vagina, 1942, with radiation.	Ileus, phlebitis, small pelvic abscess	62	Recurred in 11 months
7	Cancer of cervical stump controlled with radiation; persistent in a posterior nodule (probably undertreated).	0	25	Patient still in good health 10 months postoperatively
8	Cancer of vagina	Left ureteroperineal fistula	21	One attack of pyelitis; spontaneous improvement in fistula at 4 months.

No portion of the urinary tract was excised in 8 patients, whose cases are summarized in Table 1. It is apparent that this procedure has been used as an extended modification of the Miles operation for tumors involving the rectum, the posterior vagina or the pouch of Douglas. Although the bladder and lower ureters were completely dissected off their supporting structures, a fistula developed in only 1 case. Most patients are slow to regain the faculty of micturition, and bladder sensation may be absent for months. There were no deaths, and the recurrence rate is about what might be expected. The site of recurrence has not been adjacent to the bladder in any case; we do not believe that a total

*Presented at the annual meeting of the New England Surgical Society, York Harbor, Maine, September 22, 1951.

From the Gynecological Services of the Massachusetts General Hospital (Vincent Memorial), the Pondville Hospital (Massachusetts Department of Public Health) at Norfolk and the Palmer Memorial of the New England Deaconess Hospital.

Vital financial support for this study was supplied by an institutional grant of the American Cancer Society to the Massachusetts General Hospital.

†Clinical associate in gynecology, Harvard Medical School; assistant surgeon, Massachusetts General Hospital; gynecologist, Pondville Hospital (Massachusetts Department of Public Health).

‡Clinical professor of gynecology, Harvard Medical School; chief of staff, Vincent Memorial Hospital (the Gynecological Service of the Massachusetts General Hospital); senior gynecologist, Pondville Hospital (Massachusetts Department of Public Health); gynecologist, Palmer Memorial Hospital.

exenteration in this group would improve the rate of cure.

The bowel was spared in 11 women (Table 2). In the majority we were dealing with cancer of the cervix, persistent or recurrent after other forms of therapy or already invading the bladder (Stage IV) and therefore with less than a 4 per cent chance of cure by radiation.[3] Transplantation of both ureters into the colon was effected concomitantly in every case but 3; a nonfunctioning right ureter in two patients was once ligated and once brought out to the skin, and bilateral ureteroenterostomy preceded the extirpation in the third. It is probably fair to regard these 11 patients as examples of an extended

postoperative notes. A gratifying improvement in our ability to get these patients through the operation without severe shock and out of the hospital alive is seen. This is due, in part, to more expeditious technic and more intelligent postoperative management as the result of cumulative experience. Also important, however, has been the elimination of a perineal stage of operation in those cases in which adequate excision from above was possible. The technical steps in this modification are identical with those of the more radical combined abdominal and perineal operation up to the point at which the contents of the pelvis have been freed on all sides and from the levator muscles. If it is apparent that there

TABLE 2. *Data on 11 Patients in Whom the Bladder Was Removed and the Bowel Spared.*

Series Number	Diagnosis	Complications	No. of Days in Hospital After Operation	Subsequent Course
1	Recurrent cancer of cervix; vesicovaginal fistula.	0	41	Metastatic inguinal nodes; patient died in 2½ years, probably with disease.
2	Cancer of cervix involving bladder	Wound abscess	77	Bone metastases; patient died.
3	Cancer of cervix; metastases to vulva.	0	60	Metastatic inguinal nodes and local recurrence; patient died.
4	Cancer of cervix involving bladder	0	26	Extensive peritoneal recurrence; patient died.
5	Cancer of cervix recurrent	Fecal fistula; pyelitis; phlebitis.	Died on 64th day	
6	Cancer of cervix recurrent	0	48	Ureteral stricture; peritoneal recurrence; patient died.
7	Cancer of cervix recurrent	0	19	Recurrence; patient died.
8	Cancer of cervix involving bladder	0	21	Ureteral stricture; recurrence; patient died.
9	Cancer of cervix recurrent	0	14	Metastatic upper-abdominal nodes; patient died.
10	Cancer of urethra and bladder	Peritonitis; pyelitis.	Died on 57th day	
11	Cancer of urethra and vagina	0	50	Recurrence in pelvis; patient still living.

version of the operation of total cystectomy; the mortality and complications are of the same order of magnitude.[4] As an operation for cancer of the cervix, however, it has proved to be uniformly inadequate; every patient is now dead except one, who has recurrent disease. Recurrent or metastatic disease was demonstrated in every case, although it was not always the cause of death.

Removal of all pelvic viscera with diversion of fecal and urinary drainage was carried out 27 times. In another 8 women surgery was limited to exploration and biopsy of manifestly incurable tumors. Table 3 summarizes the indications, type of operation, severity of operation and the hospital course in the group in which resection was possible. In this group also cancer of the cervix, recurrent or advanced, was the indication. The term "severity of operation" reflects the personal opinion of these reviewers and is based on the number of transfusions on the day of surgery and the following day, the blood pressure and pulse records during the same period and the tenor of the surgeon's operative and

is an adequate margin of normal tissue below the site of disease, the levators are separated from vagina and rectum and the specimen is retracted forcibly upward and amputated through urethra, vagina and bowel. In thin or relaxed patients the vulva and anus are often easily removed by this maneuver.

The amount of blood loss and rapidity of its replacement determine whether or not shock develops during the operation. Early interruption of the internal iliac vessels with individual clamps and ligatures applied serially on the lateral branches usually permits the surgeon to mobilize the pelvic contents en masse without significant blood loss. Often there is persistent venous drip from vessels that run parallel to the pelvic wall and are thus difficult to secure. In exerting pressure over such areas one must guard against interrupting the return flow through the external iliac vein, for this may rapidly exclude from the circulation several liters of blood trapped in the lower extremity. The resultant fall in blood pressure is likely to be prolonged despite blood replacement in apparently adequate volume, and a dangerous excess of fluid

may be introduced. In Case 24 (Table 3) anesthesia was maintained by a technic of controlled hypotension.[5] It was an unqualified success, and it is planned to make further use of this important aid to surgery.

The postoperative complications (Table 3, last column) have been serious, and their management has often posed problems. There were 6 deaths. Two patients (Cases 2 and 8) succumbed to operative shock. Two others (Cases 5 and 6) died of infection developing in the wake of technical errors. The other two (Cases 3 and 4) must be considered victims of improperly functioning ureteroenterostomies with associated infection and kidney failure. The ureteroenterostomy remains our most annoying source of complication. We have employed two technics. Originally the cut end was widened by splitting it longitudinally and then implanting it 1 cm. or more inside the lumen of the bowel through a short incision. More recently we have followed the technic of Cordonnier,[6] with careful mucosa-to-mucosa approximation by interrupted fine-catgut sutures. The former procedure is more likely to result in stricture, the latter to leak and form a urinary fistula to the perineum. In 3 cases, after fistula developed (Cases 7, 12 and 15) the ureter was successfully reimplanted in another segment of bowel. In 1 patient (Case 17) in whom leaks appeared to have developed at both anastomoses, a prompt double-barreled transverse colostomy was rapidly followed by healing of the fistula; she is well today, thirteen months later, with separate urinary and fecal colostomies. Both kidneys show good function, although there is dilatation and stones have formed in the right renal pelvis.

Thrombosis of superficial or deep veins of the leg has been the only vascular complication, but we noted no episode of pulmonary embolism. Treatment with anticoagulants has been offered cautiously and without causing bleeding.

Uncontrollable electrolyte imbalance has appeared much less frequently than was anticipated;

TABLE 3. *Data on 27 Patients in Whom All Pelvic Organs Were Resected.*

Series Number	Diagnosis	Type of Operation	Severity of Operation	Complications	No. of Days in Hospital After Operation
1	Recurrent cancer of cervix	Combined abdominal and perineal	Mild	0	50
2	Cancer of cervix and separate case of sigmoid	Combined abdominal and perineal	Severe	Shock	Died on 1st day
3	Recurrent cancer of cervix	Combined abdominal and perineal	Moderate	Uremia, malnutrition	Died on 29th day
4	Cancer of cervix involving bladder	Combined abdominal and perineal	Moderate	Uremia, malnutrition	Died on 59th day
5	Recurrent cancer of cervix	Combined abdominal and perineal	Mild	Jaundice; necrosis of bowel; fistula.	Died on 17th day
6	Recurrent cancer of cervix	Abdominal	Severe	Jaundice; peritonitis; fistula.	Died on 8th day
7	Recurrent cancer of cervix	Abdominal	Moderate	Right-ureteral fistula; reimplanted in cecum.	53
8	Recurrent cancer of cervix	Abdominal	Severe	Shock	Died on 5th day
9	Recurrent cancer of cervix	Bilateral nephrostomies; abdominal.	Moderate	0	44
10	Recurrent cancer of cervix	Abdominal	Mild	0	16
11	Cancer of cervix involving bladder	Abdominal	Mild	Pyelitis	24
12	Recurrent cancer of cervix	Abdominal	Mild	Left-ureteral fistula; reimplanted into sigmoid.	46
13	Cancer of cervix involving bladder	Abdominal	Mild	Pyelitis	24
14	Recurrent cancer of cervix	Abdominal	Moderate	Phlebitis	42
15	Recurrent cancer of cervix	Abdominal	Moderate	Left-ureteral fistula; reimplanted into sigmoid.	60
16	Recurrent cancer of cervix	Abdominal	Mild	Urinary and fecal fistula	66
17	Cancer of cervix involving bladder	Abdominal	Moderate	Urinary fistula; transverse colostomy.	50
18	Recurrent cancer of cervix; fistulas	Transverse colostomy; abdominal.	Mild	Phlebitis	28
19	Carcinosarcoma of uterus and vagina	Combined abdominal and perineal	Moderate	0	24
20	Cancer of cervix involving bladder	Abdominal	Mild	Very slow to eat	58
21	Cancer of vagina	Combined abdominal and perineal	Moderate	Abscess of abdominal wall	29
22	Recurrent cancer of cervix	Abdominal	Mild	Wound abscess	51
23	Recurrent cancer of cervix	Abdominal	Moderate	0	33
24	Recurrent cancer of cervical stump	Abdominal	Very mild	0	34
25	Recurrent cancer of cervix	Abdominal	Mild	Wound abscess (major)	75
26	Recurrent cancer of cervix	Abdominal	Mild	0	16
27	Recurrent cancer of cervix	Abdominal with skin ureterostomies	Mild	0	20

in all cases it was due to renal malfunction. Small-bowel obstruction has occurred twice, long after operation and only in association with widespread recurrence of cancer.

One striking feature common to all patients is slow recovery of appetite, strength and desire to go home. Psychiatric interviews were held with several patients before and after operation; they shed some light on the mental divagations that accompany this type of profound physical and psychic insult. A skilled and sympathetic staff of nurses has been the most important single factor in the rate of recovery, once operation and its complications have been surmounted.

Discussion

Eliminating a perineal stage of operation will unquestionably reduce the mortality. Whether this will permit recurrence of cancer in patients who might otherwise have been cured is still open to question. We have no case in which we have left disease, limited to this area. Although one occasionally sees cases of cancer of the cervix or uterus with microscopic infiltration of the lymphatics of the vagina at a distance from the gross tumor, the natural development of most untreated lesions is one of lateral spread and permeation of the lymphatics draining along the branches of the internal iliac vessels. On theoretical grounds one can assume that the advantages of this operative modification outweigh the disadvantages.

The complications of ureteroenterostomy have inspired several variations in the management of the urinary tract, but none offers real promise of improvement. Skin ureterostomies have the advantage that one knows immediately when a kidney is not functioning properly, a condition that may escape notice for a long time if the ureter is emptying into the large bowel. Many skin ureterostomies require tender care, however, and the patient who also has a fecal colostomy may find that considerable time must be devoted to self-attention. Much remains to be learned about this phase of the operation. At present it is not possible to construct an anastomosis that is always watertight, creates no back pres-

Table 4. *Patients in Whom All Pelvic Organs Were Resected and Who Survived Operation Over Nine Months.*

Series Number	Length of Follow-up	Status of Cancer	Status of Urinary Tract
	yr.		
1	3 6/12	0	Satisfactory
7	1 10/12	0	Satisfactory
9	1 8/12	Recurrence in five months. Dead	Ureteroenterostomy did not drain well; nephrostomies successful.
10	1 4/12	0	Right ureter satisfactory; increasing dilatation of left ureter.
11	1 4/12	0	Satisfactory
12	1 3/12	0	Satisfactory
13	1 3/12	Recurrence in three months. Dead	Satisfactory
14	1 3/12	Metastatic nodes of right groin resected. Living	Left ureter satisfactory; hydronephrosis of right side.
15	1 2/12	Recurrence in two months. Dead	Satisfactory
16	1 2/12	0	Spontaneous slow closure of ureteroperineal fistula; ureters satisfactory.
17	1 2/12	0	Left ureter satisfactory; hydronephrosis and calculi of right side.
18	1	0	Satisfactory
19	11/12	Recurrence in two months. Dead	Satisfactory
20	11/12	Recurrence in three months. Dead	Satisfactory
21	11/12	0	Nonfunctioning left kidney; hydronephrosis and calculi of right side.
22	11/12	0	Satisfactory
23	10/12	0	Bilateral nonfunction. Nephrostomy. Died in uremia.
24	9/12	0	Satisfactory
25	9/12	Recurrence in one month. Dead	Satisfactory

Twenty-five patients were treated more than nine months ago. The 19 who lived are listed in Table 4, with data on the length of follow-up and the status of their disease and of the urinary tract. Recurrence of cancer has appeared in 7, but in 6 of these patients it was known that cure had not been accomplished at the time of operation.

Eight patients (Cases 1, 7, 11, 12, 16, 18, 22 and 24) are alive, healthy and living essentially the same life as before, although 1 (Case 16) had developed a perineal urinary fistula after operation that healed and recurred over the course of several months. It has remained healed, and the pyelogram shows good function without dilatation.

The other 4 women who have thus far escaped recurrence of disease have had serious interference with urinary drainage from one or both sides; one has died in renal failure.

sure against the kidney and also prevents reflux of bowel content up the ureter. Our effort at present is therefore directed to producing a connection that does not leak or develop stricture, on the assumption that such an arrangement would result in less rapid destruction of kidney parenchyma.

Conclusions

Surgical removal of the contents of the female pelvis posterior to the urinary tract can be accomplished with a low morbidity and mortality. It may cure the disease when the tumor is primary in the rectum, the posterior vagina, or the pouch of Douglas.

Surgical removal of the contents of the female pelvis anterior to the bowel was an inadequate operation for cancer of the cervix in the group we selected. Others[7] have reported more success, however.

The mortality following removal of all pelvic organs can be kept below 10 per cent if a perineal stage of operation is avoided in selected cases. It is too early to decide whether or not this modification will decrease the rate of cure.

The major problem centers on the management of the urinary tract. Our conclusions in this matter are identical with those reported by Parsons and Leadbetter.[8] Surgeons interested in this field must continue as at present[1, 2, 4, 9] to modify and improve their technics until a solution is found.

Despite the decrease in morbidity and mortality, there is at this time no justification for a change in the indications for surgery of this magnitude. It should be limited to patients in whom the chance of cure by any other form of therapy is less than 5 per cent.

References

1. Brunschwig, A., and Pierce, V. K. Partial and complete pelvic exenteration. *Cancer* **3**:972-974, 1950.
2. Parsons, L., and Bell, J. W. Evaluation of pelvic exenteration operation. *Cancer* **3**:205-213, 1950.
3. Morris, J. M., and Meigs, J. V. Carcinoma of cervix: statistical evaluation of 1,938 cases and results of treatment. *Surg., Gynec. & Obst.* **90**: 135-150, 1950.
4. Colby, F. H., and Kerr, W. S., Jr. Carcinoma of bladder. *New Eng. J. Med.* **244**:504-506, 1951.
5. Gillies, J. Anaesthetic factors in causation and prevention of excessive bleeding during surgical operations. *Ann. Roy. Coll. Surg.* **7**:204-221, 1950.
6. Cordonnier, J. J. Ureterosigmoid anastomosis. *Surg., Gynec & Obst.* **88**:441-446, 1949.
7. Brunschwig, A., Jordan, M. J., and Pierce, V. K. Radical panhysterectomy, pelvic lymph node excision, total vaginectomy, and total cystectomy; one-stage operation for carcinoma of female genitals invading bladder (report of 21 cases). *Am. J. Obst. & Gynec.* **59**:237-245, 1950.
8. Parsons, L., and Leadbetter, W. F. Urologic aspects of radical pelvic surgery. *New Eng. J. Med.* **242**:774-779, 1950.
9. Bricker, E. M., and Modlin, J. Role of pelvic evisceration in surgery. *Surgery* **30**: 76-94, 1951.

THE EFFECTS OF ACTH AND OF CORTISONE ON THE PLATELETS IN IDIOPATHIC THROMBOPENIC PURPURA*

Bernard M. Jacobson, M.D.,† and William D. Sohier, M.D.‡

BOSTON

THE following case reports illustrate the dramatic effects of ACTH and of cortisone on the platelets in 3 patients with idiopathic thrombopenic purpura.

Case Reports

Case 1. C. I. (No. 13998), a 59-year-old woman, was first admitted to the Massachusetts General Hospital in March, 1945, with idiopathic thrombopenic purpura of several years' duration. Because of increasing purpura a splenectomy was performed, with marked improvement. In January, 1946, the patient underwent an uncomplicated cholecystectomy for cholelithiasis. She suffered no recurrent symptoms until the summer of 1950, when petechiae and later ecchymoses developed over her legs and trunk. For two months prior to November 16, 1950, she had been given aspirin, aloin, thyroid, atropine, phenobarbital, Sulphocol and Salicionyl by her local physician as treatment for pain and swelling of the left knee. Despite omission of all these drugs the purpura increased, until she was admitted to the hospital on December 8, 1950. On admission to the hospital the patient exhibited numerous purpuric spots over both legs, the left arm and the lower back. The only abnormality of the blood constituents was a platelet count of 25,000 per cu. mm.§ A bone-marrow aspirate revealed an abundant number of megakaryocytes without evidence of platelet formation. The patient was then given ACTH (Armour), 100 mg. intramuscularly daily for 5 days, followed by 25 mg. daily for 5 days. Figure 1 shows the platelet response, exhibiting a peak of 580,000 per cu. mm. on the 5th day of treatment. On the 9th day of treatment a repeat bone-marrow aspiration showed abundant platelets at the periphery of the megakaryocytes. She was discharged on 25 mg. of ACTH intramuscularly every other day. However, 2 days after discharge an upper-respiratory infection and pain in the left knee developed, and she resumed the ingestion of aspirin. The purpura reappeared a few hours later. On readmission to the hospital eight days later, on December 28, 1950, she exhibited a generalized purpuric rash, fever of 103°, nasal congestion and a slightly swollen, painful left knee. A platelet count showed only 21,000 per cu. mm. ACTH was resumed in a dose of 100 mg. intramuscularly daily, with a prompt rise in platelets, as shown in Figure 1. This dosage was maintained for 9 successive days, followed by 50 mg. daily for 4 days. The platelet count reached 2,000,000 per cu. mm. on the 13th day of treatment; at this time the medication was omitted. At the time of discharge from the hospital on January 19, 1951, the 8th day after cessation of treatment, the temperature was normal and the rash had

*From the Medical Service, Massachusetts General Hospital, and the Department of Medicine, Harvard Medical School.

This investigation was supported by a grant from the Lederle Laboratories Division, American Cyanamid Company.

†Instructor in medicine, Harvard Medical School; assistant physician and head of Anemia Clinic, Massachusetts General Hospital.

‡Resident in medicine, Massachusetts General Hospital.

§The platelets were estimated in the following manner: A small drop of capillary blood was collected on a cover slip and was then inverted on a slide coated with a thin layer of brilliant cresyl blue. The erythrocytes were counted in another drop of capillary blood. Under the oil-immersion objective the platelets among 1000 erythrocytes in various parts of the supravitally stained smear were counted and this number was multiplied by the red-cell count/1000, yielding the number of platelets per cu. mm. By this method, platelet counts in normal persons range from approximately 500,000 to 1,000,000 per cu. mm.

disappeared; the platelets numbered 1,400,000 per cu. mm. The patient was followed at weekly intervals for 1 month after discharge; she was taking no medication. The platelets remained at high levels; on February 16, 1951 (the 28th day after cessation of treatment), they numbered 1,340,000. By March 9, 1951 (the 49th day, after cessation of treatment), they had receded to 200,000. One week later they dropped farther to purpuric levels; they have remained at low levels to the present time.

Because of the possible relation between the ingestion of aspirin and the onset of the purpura, in the anamnesis, on

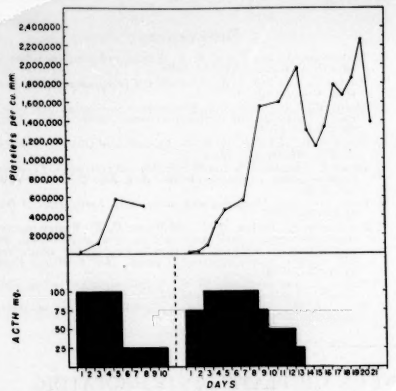

FIGURE 1. *The Effects of ACTH on the Platelet Level in Case 1. An interval of ten days separates the two periods.*

the 6th day after cessation of treatment, 8 gm. of aspirin was given over a 48-hour period, with no significant change in the platelet level.

CASE 2. E. C. (No. 316061), a 43-year-old postal clerk, first noted purpura in 1943, while serving with the Armed Forces. For the next 5 years he suffered intermittent episodes of ecchymoses on the legs, nosebleeds and hemoptysis. In January, 1948, he was admitted to a naval hospital because of massive hemoptysis. The platelet count was found to be 30,000 per cu. mm. The diagnosis of idiopathic purpura hemorrhagica was established. After a second hemoptysis splenectomy was performed, with prompt rise of platelets to over 100,000 per cu. mm. and cessation of bleeding. In December, 1949, the purpura recurred. The patient presented himself at the Massachusetts General Hospital Out Patient Department in January, 1950, with several large ecchymoses on the left leg. A Grade II systolic murmur was heard over the entire precordium; the blood pressure was 180/115. Physical examination was otherwise negative. The positive laboratory findings included a bleeding time of over 20 minutes, a positive tourniquet test and a platelet count of 64,000 per cu. mm. On January 29, 1951, he came to the Emergency Ward of the Massachusetts General Hospital because of pain, swelling and discoloration of the left ankle persisting one week after a "minor twist." X-ray films revealed no fracture. On physical examination the left leg up to mid-calf was diffusely tender, swollen and greenish-blue in color. A platelet count showed a value of 20,000 per cu. mm. The patient was then given 25 mg. of ACTH intramuscularly every 6 hours, for 2 days, with a rise in platelets, as shown in Figure 2. Two days later he was discharged on 25 mg. of ACTH daily but was readmitted after 4 days, on February 6, with little change in the appearance of the left leg and with a platelet count of 50,000 per cu. mm. At this point cortisone was administered in a dose of 100 mg. by mouth every 8 hours, followed by a rise of platelets to 1,000,000 per cu. mm. on the 4th day of treatment, as shown in Figure 2. However, over the following week, with the cortisone dosage being gradually decreased to 50 mg. daily, the platelet count fell to 27,000 per cu. mm. The left leg improved markedly. When seen on February 23, the 7th day after cessation of treatment, the patient was asymptomatic. The leg appeared normal. The platelet count was 14,000 per cu. mm. Since this time the platelets have remained at purpuric levels.

CASE 3. J. T. (No. 740382),* a 32-year-old man, was admitted to the hospital on June 6, 1951, with a history of purpura of 7 years' duration. Careful study by his physician during the past year had established consistently low platelet levels. The physical examination revealed no significant

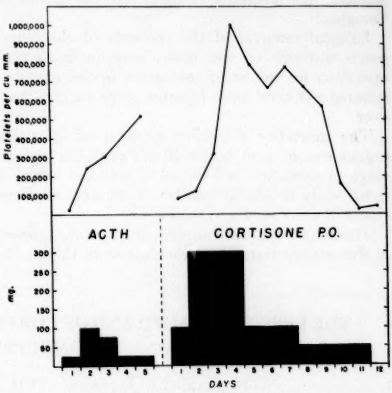

FIGURE 2. *The Effects of ACTH and of Cortisone on the Platelet Level in Case 2. An interval of four days separates the two periods.*

abnormalities other than a purpuric rash over the lower extremities. The platelets numbered 59,000 per cu. mm., and megakaryocytes without platelet formation were present in the bone-marrow aspirate in normal numbers. On June 9, the platelets again numbered 60,000 per cu. mm.; on this day cortisone, 300 mg. by mouth daily, was administered, followed by a sharp rise in the platelet level to 410,000 per cu. mm. on the 4th day of treatment (Figure 3). At this point the cortisone was omitted. On the following day splenectomy was performed. After splenectomy the platelets continued to rise in the usual fashion, ascending to around 2,000,000 per cu. mm. on the 3rd postoperative day.

DISCUSSION

Changes in the hematopoietic system after the administration of ACTH or of cortisone have been studied by several investigators and have been summarized by Wintrobe.[1] In addition to the well known diminution in the number of circulating eosinophils and of lymphocytes, more recent observations by Finch and others[2] demonstrate transient rises in the erythrocyte level and in the number of neutrophils. References in the literature to the effects of these hormones on platelet formation in-

*These observations have been made through the courtesy of the patient's physician, Dr. Robert L. Richards, of the Ellsworth Medical Group, Chester, Vermont.

clude the statement by Wintrobe[1] that "in the case of purpura hemorrhagica the bleeding time and the clot retraction returned temporarily to normal as the platelet count rose." Specific details of two cases of thrombopenic purpura are noted by Robson and Duthie[3]; in their Case A only 100 mg. of ACTH was administered over two days; the platelets rose gradually from a level of about 10,000 to about 150,000 per cu. mm. seven days after the last dose and then rapidly fell; a similar rise followed the administration of 200 mg. of ACTH over two days in the same case. In their Case B, after treatment with 340 mg. of ACTH over three days similar changes in the platelets took place.

In contrast to the platelet changes described by Robson and Duthie,[3] the present observations revealed sharp rises in the platelet levels, beginning on the second to the fourth day of treatment after administration of ACTH parenterally and cortisone by mouth. From this limited number of observations no definite conclusions can be drawn concerning the relative effects of the two hormones on either the rate of initial platelet formation or the duration of maintenance of a high platelet level after the omission of the hormone.*

The three cases described above indicate that in both the presence and the absence of the spleen platelet formation in idiopathic thrombopenic purpura can be stimulated by ACTH and by cortisone. On the other hand, this effect may not be observed in all cases of thrombopenic purpura. Such a case is one of severe thrombopenia associated with the histologic picture of cirrhosis of the liver in a 62-year-old woman (L. F., No. 303714). Neither ACTH nor cortisone exerted any effect on the platelet level. On the other hand, splenectomy also was followed by no significant change in the number of platelets, despite the presence of a hyperplastic bone marrow with abundant megakaryocytes.

Finally, it is evident that both ACTH and cortisone may have practical therapeutic significance under two conditions. Either hormone may be useful in preparing the patient for splenectomy so that the operation can be performed in the presence of a normal number of platelets of endogenous origin. Secondly, if for one reason or another splenectomy is not indicated or if the spleen has already been removed, either hormone may tide the patient over a critical bleeding episode.

Summary

The administration of ACTH and of cortisone in 3 patients with idiopathic thrombopenic purpura was followed by prompt increases of platelets from purpuric levels to normal and even to abnormally high levels.

These hormones may prove useful in preoperative preparation for splenectomy and in the temporary restitution of platelets to a normal level during a bleeding episode.

*Rises in platelet counts under the influence of ACTH and cortisone are undoubtedly accompanied by changes in capillary permeability. This was clearly described by Robson and Duthie.[3] More recently similar changes in the blood vessels of the rabbit ear have been reported by Ebert,[4] and changes in vascular fragility in 4 cases of thrombopenic purpura have been recently described by Faloon and others.[5]

Addendum

Since this paper was submitted for publication more extensive observations have appeared on the same subject by Bethell, Miller and Myers.[6] Six

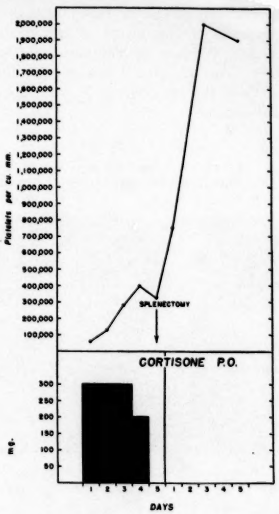

FIGURE 3. *The Effects of Cortisone and of Splenectomy on the Platelet Level in Case 3.*

cases of idiopathic thrombopenic purpura treated with ACTH or with cortisone responded with rises in platelet counts; in several cases the remissions persisted months after the completion of treatment.

References

1. Wintrobe, M. M. ACTH and cortisone in hemopoietic disorders. *Am. J. Med.* 9:715-717, 1950.
2. Finch, S., Crockett, C. L., Jr., Stout, C. F., Ross, J. F., and Bayles, T. B. Haematological effects in patients with rheumatic diseases treated with ACTH and cortisone. *Ann. Rheumat. Dis.* 9:398, 1950.
3. Robson, H. N., and Duthie, J. J. R. Capillary resistance and adrenocortical activity. *Brit. M. J.* 2:971-977, 1950.
4. Ebert, R. H. Changes in connective tissue reaction induced by cortisone — in vivo observations using rabbit ear chamber technique. *J. Clin. Investigation* 30:636, 1951.
5. Faloon, W. W., Greene, R. W., and Lozner, E. L. Hemostatic defect in thrombocytopenia as studied by use of ACTH and cortisone. *J. Clin. Investigation* 30:638, 1951.
6. Bethell, F. H., Miller, S., and Myers, M. C. *Proceedings of the Second Clinical ACTH Conference.* Edited by J. R. Mote. Vol. 2. *Therapeutics.* Philadelphia: The Blakiston Company, 1951. Pp 173-181.

SOLITARY JEJUNAL METASTASIS TWENTY YEARS AFTER REMOVAL OF A RENAL-CELL CARCINOMA*

Report of a Case

ARNOLD STARR, M.D.,† AND GERALD M. MILLER, M.D.‡

BOSTON

IT IS well known that metastasis from a carcinoma of the kidney may occur many years after removal of the primary tumor.[1-3] The following example is reported because of the extraordinary interval between removal of the primary tumor and its recurrence and because of the unusual site of the metastasis. An additional feature of interest in this case was the occurrence of other benign and malignant tumors.

CASE REPORT

Mrs. E. A. (B.I.H. No. 18596) was 52 years old when she had a right nephrectomy in September, 1931, for a hypernephroma. The symptoms and signs were of 8 months' duration. At that time the patient also had hypertension (200/100) and a calcified uterine leiomyoma.

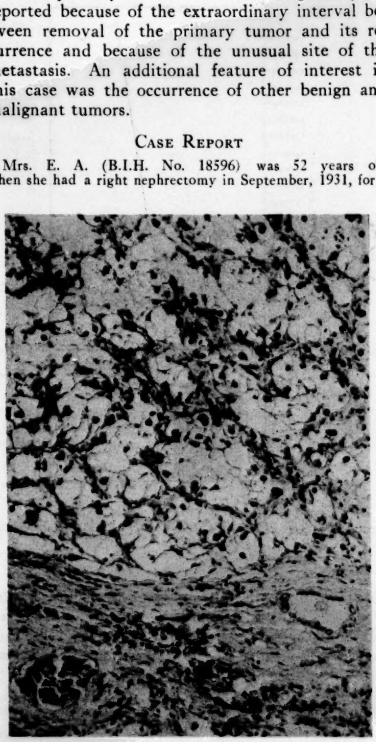

FIGURE 1. *Clear-Cell Carcinoma of Kidney. Slide shows glomerulus and cross-section of tubule in surrounding fibrosed renal parenchyma (x100).*

The kidney measured 9 x 9 x 6 cm. and had a large tumor in its upper anterior surface. The tumor was firm; its cut surface bulged and was yellowish-pink in color. There was extensive invasion of the renal pelvis and cortex by the tumor, but the renal capsule was not invaded. The renal vein and its tributaries revealed no tumor. Microscopical examination showed a typical renal carcinoma of the "clear-cell" type. Delicate fibrous strands separated masses of pale cells with clear cytoplasm and definite cell borders. The cells were oval, round and polyhedral, with small oval nuclei and well defined nucleoli. In some places cells appeared to form imperfect glands or tubules. Areas of necrosis, hemorrhage and inflammation were also noted. Inflammation and fibrosis were present in that part of the kidney not involved by tumor (Fig. 1).

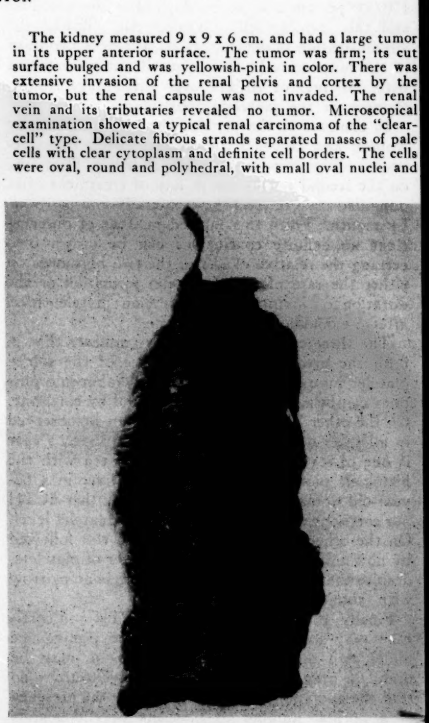

FIGURE 2. *Photograph of Resected Jejunum and Polypoid Tumor.*

The patient enjoyed good health, except for a thyroidectomy performed in 1937 for a fetal adenomatous nodule, until 1942, when melena occurred.

Examination in March, 1943, revealed no significant abnormalities except hypertension (210/130) and x-ray evidence of a large round polypoid mass in the mid-sigmoid region. A laparotomy disclosed two papillary tumors of the sigmoid portion of the bowel, a large tumor of the right ovary and a calcified uterine leiomyoma. No peritoneal metastases were noted. Sigmoid resection was performed and the right ovarian tumor was excised. The segment of bowel contained two papillary masses, one 3.5 cm. in diameter with a 2-cm. base

*From the Departments of Surgery of Tufts College Medical School Harvard Medical School and the Beth Israel Hospital.

†Clinical professor of surgery, Tufts College Medical School; instructor in surgery, Harvard Medical School; visiting surgeon, Beth Israel Hospital.

‡Formerly, assistant resident in surgery, Beth Israel Hospital.

and the second, 4.5 cm. from it, 1.25 cm. in diameter with a 5-cm. base.

Microscopical examination of these masses revealed two well differentiated papillary neoplasms, which had begun to invade the muscularis mucosae. The tumor cells were arranged in long papillary fronds of regular glands with closely packed columnar cells of intestinal origin. They did not resemble the large clear cells of the renal tumor. The diagnosis was papillary adenocarcinoma of the large intestine.

The ovarian tumor weighed 4500 gm., was cystic in its center and was diagnosed as edematous ovarian fibroma.

The patient was well until October, 1950, when she began to feel weak and had episodes of palpitation. She was obese. The skin showed numerous pigmented and papillary nevi not present on earlier examinations. The blood pressure was 170/110. Examination was otherwise not remarkable, except for secondary anemia (hemoglobin 9.7 gm.) and occult blood in the stool. A barium-enema examination was negative, but small-bowel studies showed a partially obstructing lesion in the mid-jejunum suggesting a polypoid intestinal tumor with surface ulceration.

Exploration of the abdominal cavity on February 23, 1951, revealed a polypoid mass in the mid-jejunum. The leiomyoma of the uterus noted at the previous operation was unchanged. There was no other evidence of neoplasm in the peritoneal cavity. The right renal fossa was free of disease. The jejunal tumor was resected and intestinal continuity was re-established. The postoperative course was uneventful.

The resected jejunum showed a broad-based reddish polypoid tumor projecting 2 cm. from the mucosa (Fig. 2). The base of the lesion measured 2 x 2 cm; on cut section the tumor was seen to have invaded the submucosa.

Microscopical examination revealed a "clear-cell" renal tumor involving the submucosa and mucosa of the bowel and projecting above the mucosa. Its structure was the same as that of the kidney tumor removed 20 years earlier — masses of large clear cells with well defined walls, small nuclei and prominent nucleoli, separated by fibrous-tissue strands and in some areas forming imperfect glands or tubules (Fig. 3).

Discussion

Renal carcinomas most commonly metastasize to bone,[1-5] brain and lung, sometimes to skin, gall bladder, bile ducts, corpus cavernosum, epididymis, bowel, pancreas, thyroid gland, pericardium, heart, mediastinum, seminal vesicles, mouth, external auditory meatus and phalanges. Excision of a single metastasis in an accessible site may afford a long respite from the disease. A fourteen-year survival has been reported after removal of a solitary intracranial metastasis,[11] and an eighteen-year survival has been recorded after pulmonary lobectomy for a solitary metastasis.[12, 13]

Metastases appearing for the first time ten, twelve and even sixteen years after nephrectomy have been reported.[6-8] The twenty-year interval preceding the appearance of metastasis in our case and in the case reported by Graves[9] is very rare.

All types of metastases to the intestine involve the small bowel more often than the large, and are usually multiple. In addition to the usual sites of metastases, Willis[10] described bloodborne implantation in the submucosa of the intestine producing flat, sessile nodules that may grow into pedunculated tumors. These may produce intussusception or bleeding from ulceration of the surface. In our case a severe anemia resulted and was the presenting feature in the clinical picture.

Summary

A case of renal carcinoma is presented in which metastasis was disclosed twenty years after the removal of the primary tumor. The solitary polypoid jejunal metastasis gave rise to anemia and occult bleeding in the stool. An additional aspect of this case was the occurrence of other benign and malignant neoplasms involving the thyroid gland, ovary, skin, uterus and bowel.

Figure 3. *Identical Pattern of Jejunal Metastasis with Tumor Shown in Figure 1 (x100).*

The authors are indebted to Dr. David Hausman for assistance in the preparation of the pathological data.

References

1. Lowsley, O., and Kirwin, T. J. *Clinical Urology.* 2 vol. 1791 pp. Baltimore: Williams & Wilkins Company, 1944.
2. Colby, F. H. *Essential Urology.* 580 pp. Baltimore: Williams & Wilkins Company, 1950.
3. Deming, C. L. Prognosis and problems in renal tumors. *J. Urol.* **55**:571-582, 1946.
4. Graham, A. P. Malignancy of kidney: survey of 195 cases. *J. Urol.* **58**:10-21, 1947.
5. Abeshouse, B. S., and Weinberg, T. Malignant renal neoplasma: clinical and pathologic study. *Arch. Surg.* **50**:46-55, 1945.
6. Clairmont, P. Ueber ein Hypernephrom-impfrecidiv in den Bronchiallymphdrüsen. *Arch. f. klin. Chir.* **73**:620-636, 1904.
7. Fischer, B. Demonstrationen: Perforation der Aorta. Aneurysmatische Erweiterung der Aorta. Hypernephrommetastasen 6½ Jahre nach Exstirpation. *München. med. Wchnschr.* **57**:101, 1910.
8. Broster, L. R. Hypernephroma. *Proc. Roy. Soc. Med.* **23**:551, 1930.
9. Graves, R. C., and Mabrey, R. E. Adenocarcinoma of kidney, recurrent after twenty years. *New Eng. J. Med.* **212**:416, 1935.
10. Willis, R. A. *The Spread of Tumors in the Human Body.* 550 pp. London: J & A. Churchill, Ltd., 1933.
11. Stortebecker, T. P. Metastatic hypernephroma of brain from neurosurgical point of view: report of 17 cases. *J. Neurosurg.* **8**:185-197, 1951.
12. Barney, J. D. Twelve-year cure following nephrectomy for adenocarcinoma and lobectomy for solitary metastasis. *J. Urol.* **52**: 406, 1944.
13. Castleman, B. Personal communication.

TISSUE NECROSIS FOLLOWING SUBCUTANEOUS INFILTRATION WITH NOR-EPINEPHRINE*

Report of Two Cases

H. P. GREENWALD, M.D.,† A. GOOTNICK, M.D.,‡ N. M. LUGER, M.D.,§ AND J. A. KING, M.D.¶

BROOKLYN, NEW YORK

NOR-EPINEPHRINE has recently come into wide use in the treatment of hypotensive states of medical or surgical origin.[1-4] Review of the literature does not reveal any reports of adverse skin reaction, with one exception: Deterling and Apgar[5] allude briefly to minor ulceration following the infiltration of tissues with nor-epinephrine. Among the 55 patients who have received nor-epinephrine in this hospital, 2 have recently been observed in whom extensive necrosis developed within forty-eight hours after subcutaneous leakage of nor-epinephrine from an intravenous infusion. The purpose of this report is to warn physicians of this reaction and to suggest an expedient for averting it.

CASE REPORTS

CASE 1. S. A., a 56-year-old man, had survived a myocardial infarction a year previously. On May 25, 1951, he was admitted to the emergency ward of another hospital in acute pulmonary edema. He was treated with morphine, phlebotomy and oxygen given by pressure mask combined with ethyl-alcohol inhalation. Soon after admission the patient lapsed into shock, the blood pressure falling from normal levels to 80/40. Nor-epinephrine in a concentration of 16 microgm. per cc. was infused into a surgically exposed vein at the right ankle. Infiltration of the solution into the tissues around the needle was soon noted but was not thought to require special therapy. Within 48 hours dusky, mottled discoloration had involved the entire anteromedial aspect of the leg and multiple bullous lesions had developed over the same area. The leg was cold to the touch.

The patient was transferred to the Brooklyn Veterans Hospital on the 4th day of his illness. Subsequently, serial electrocardiograms confirmed the initial impression that the pulmonary edema and the vascular collapse had been manifestations of a fresh myocardial infarction. The patient did well after the stormy early course. With conservative topical therapy consisting of pressure dressings with petrolatum gauze, there was progressive epithelialization of the denuded area until only a thick, sharply demarcated central eschar was left, measuring approximately 12 by 8 cm. At the time of the patient's discharge from the hospital it was apparent that healing would be complete without plastic repair.

CASE 2. A. J. T., a 40-year-old man, was known to have had heart disease since 1943, when he had sustained a myocardial infarction. He was admitted to the Brooklyn Veterans Hospital on May 17, 1951, because of severe lasting retrosternal pain, profuse diaphoresis and weakness. He had been having similar but more transitory bouts of chest pain for several days prior to admission. Significant physical findings included moderate distention of neck veins, cardiac enlargement, a Grade III harsh apical systolic murmur and a protodiastolic apical gallop. The pulse was 120. The blood pressure was 144/100. The liver edge was felt 3 cm. below the right costal margin and was tender.

Serial electrocardiograms revealed evidence of previous posterior infarction and intermittent auricular tachycardia but no definite indications of fresh myocardial injury. The patient was treated with bed rest, digitalis and anticoagulant therapy. His course was punctuated by repeated episodes of anterior mid-chest pain and peripheral vascular collapse at intervals of several days. One such bout was followed by moderate hemoptysis. Although pulmonary embolism was suspected, the lung fields were clear on examination and x-ray films of the chest showed no abnormal densities. No peripheral thrombosis could be detected and there was adequate prothrombin depression.

FIGURE 1. *Right Leg of Patient A. J. T. on the Third Day after Infiltration with Nor-Epinephrine.*

On June 6, 3 weeks after his admission to the hospital, the patient suffered a particularly severe attack of the same retrosternal pain and went into shock, with the blood pressure falling to imperceptible levels. Nor-epinephrine (16 microgm. per cc.) was given intravenously, and the blood pressure rose promptly. There was considerable infiltration of the solution into the tissues of the right ankle. Initially, cold packs were applied to the area of infiltration with the intention of minimizing any inflammatory reaction that might develop. It was soon realized, however, that vasoconstriction caused

*From the Cardiovascular Section, Brooklyn Veterans Administration Hospital.

Sponsored by the Veterans Administration and published with the approval of the chief medical director. The statements and conclusions published by the authors are a result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

†Senior resident in medicine, Brooklyn Veterans Administration Hospital.

‡Chief of Cardiovascular Section, Brooklyn Veterans Administration Hospital.

§Attending physician, Brooklyn Veterans Administration Hospital.

¶Resident in medicine, Brooklyn Veterans Administration Hospital.

by nor-epinephrine was more to be feared than the usual inflammatory response to a chemical irritant. Accordingly, the cold packs were replaced by warm applications, which were continued for the next 18 hours. Within 48 hours an extensive lesion had developed over most of the right leg, with serous and hemorrhagic bullae covering an edematous tender red base. The involved area was cold to the touch. This lesion was in all respects like that of S. A. (Case 1), who was in the hospital at the same time.

The bullae were debrided, pressure dressings with petrolatum gauze were applied and penicillin was given. The patient improved thereafter and appeared to be recovering, but on June 27 he again abruptly went into shock and coma. He did not respond to therapy, and died the next day. Severe coronary insufficiency, recurrent pulmonary embolism and ball-valve thrombus intermittently occluding the mitral valve were considered among the possible causes of the repeated attacks of chest pain and shock.

At autopsy an old posterior-wall infarction was found, as well as generalized coronary-artery atherosclerosis of extreme degree, with many points of marked narrowing. A single pulmonary infarction was found in the right lung. The involved skin of the right ankle was denuded of stratified squamous epithelium and the underlying cutis was diffusely infiltrated with polymorphonuclear leukocytes.

Discussion

The chance circumstance that both patients were in the hospital at the same time emphasized the similarity of their lesions. In both cases the earliest indication of skin necrosis was noted within forty-eight hours after infiltration with nor-epinephrine. In both patients large serous or hemorrhagic bullae developed on a dusky, edematous base that was distinctly colder than the surrounding uninvolved skin. The appearance was strikingly similar to acute frostbite and suggested that the local vasoconstrictor effect of nor-epinephrine was the essential causative factor.

Apparently this is not the only factor, for we have observed 3 other patients in whom subcutaneous infiltration with nor-epinephrine was not followed by adverse effects. In one of these transitory local blanching did occur, but no skin lesion developed. Another of these patients was febrile, and it is possible that the local vasoconstrictor effects of nor-epinephrine were in his case sufficiently modified by fever to avert tissue necrosis.

It is not clear to us why some patients develop necrotic lesions after infiltration with nor-epinephrine and others do not. In Case 1 no local applications were used over the infiltrated area. In Case 2 cold packs were used early, and it is possible that these had contributed to the tissue damage. Differences in individual susceptibility to nor-epinephrine, in local concentration of the drug and in speed of blood circulation may affect developments in the infiltrated tissues. It may be significant that in the patients who developed necrosis the emergency that indicated the use of nor-epinephrine was not merely a transitory period of vascular collapse in a basically sound circulatory system; these patients suffered protracted shock complicating severe myocardial injury, with prolonged reduction in cardiac output and slowed circulation through the extremities. In these circumstances, infiltration of tissue with a given quantity of nor-epinephrine may well produce a more lasting and destructive effect.

Except for the prophylactic use of penicillin, our treatment with nor-epinephrine infiltration was essentially local and protective. The use of nitrites, mecholyl or other systemic vasodilator measures is contraindicated by the already established peripheral vascular paralysis for which nor-epinephrine is given. Topical vasodilator measures, such as histamine iontophoresis or glyceryl trinitrate gel, may prove helpful, provided that they are applied promptly after infiltration, before tissue damage has occurred. However, even such local applications are not free from the danger of systemic vasodilator effect and aggravation of shock.

Because of the seriousness of the lesions and the occasional need of maintaining nor-epinephrine infusion continuously for several days, it is recommended that extravasation be prevented by administering the solution through polyethylene tubing advanced well into the vein and secured in place. Thus far, in those patients who have received nor-epinephrine by this method no infiltration has been observed.

Addendum

A third case of extensive tissue necrosis caused by nor-epinephrine infiltration has recently come to our attention. This patient, like the two here reported, had grave impairment of the circulatory system and died of congestive failure. The nor-epinephrine used in treating this patient was not from the same batch used in treating patient A. J. T. Patient S. A. received his nor-epinephrine in a different hospital, and the drug given him came from still another lot; thus these three patients with tissue necrosis received nor-epinephrine from three different lots. Moreover, in our earlier experience with the drug we observed occasional transitory local blanching after infiltration, without subsequent tissue necrosis. It seems, therefore, that the lesions described were not caused by impurities in a particular batch of the drug but developed from adverse effects of its intrinsic vasoconstrictor property.

References

1. Goldenberg, M., Pines, K. L., Baldwin, E. de F., Greene, D. G., and Roh, C. E.: Hemodynamic response of man to nor-epinephrine and epinephrine and relation to problem of hypertension. *Am. J. Med.* 5:792-806, 1948.
2. Goldenberg, M., Apgar, V., Deterling, R. A., Jr., and Pines, K. L. Nor-epinephrine (arterenol, sympathin N) as pressor drug. *J. A. M. A.* **140**:776-778, 1949.
3. Fremont, R. E., Luger, N. M., and Surks, D. E. Unpublished data.
4. Luger, N. M., Kleiman, A., and Fremont, R. E. Treatment of shock with arterenol. *J. A. M. A.* **146**:1592, 1951.
5. Deterling, R. A., Jr., and Apgar, V. Use of nor-epinephrine (L-arterenol) as pressor drug with special reference to thoraco-lumbar sympathectomy. *Ann. Surg.* **133**:37-43, 1951.

MEDICAL PROGRESS

DIGITALIS POISONING AND ITS TREATMENT (Concluded)

BURTON M. COHEN, M.D.*

ROCHESTER, NEW YORK

Because digitalis preparations, acetylcholine or vagal stimulation may cause identical electrocardiographic changes in normal persons,[113] early efforts were directed toward vagal paralysis with atropine. In fact, some experimental data purported to show that atropine might aid in modifying the myocardial lesions produced by digitalis.[69] Clinical results were conflicting. Resnik observed a reversion to regular sinus rhythm from digitalis-induced auricular fibrillation within sixty-eight minutes after a hypodermic injection of 2 mg. of atropine[75]; Gold and Otto described similar success in interrupting 5 cases of digitalis bigeminy.[43] On the other hand, Robinson and Wilson could not modify the toxic effects of digitalis in laboratory animals by vagal section,[65] nor was Reid able to influence the course of 5 patients in whom ventricular tachycardia appeared during the treatment of auricular fibrillation.[92]

The dangers inherent in the joint use of quinidine and digitalis have been mentioned, with some emphasis on the stated unpredictability of the combination.[40] These effects of quinidine vary, not only with its dose but with the intensity of the digitalis poisoning; that is, if digitalis causes ventricular tachycardia alone, quinidine may restore regular sinus rhythm, whereas if auriculoventricular block is also present quinidine may induce ventricular standstill.[40] Despite these observations, quinidine has been recommended during the administration of digitalis to prevent the onset of auricular fibrillation,[38] and in laboratory animals it did seem to exert a favorable influence.[36, 37] Gouley and Soloff reported the use of quinidine in 2 cases of ventricular and nodal tachycardia due to digitalis. In 1 patient 1.2 gm. of quinidine was successful in interrupting the arrhythmia; failure in the second case was attributed to inadequate dosage.[39] These authors conclude that although "quinidine may be contraindicated in congestive heart failure and cardiac enlargement, one must choose the lesser of evils." Freundlich employed quinidine successfully in two cases of paroxysmal ventricular tachycardia due to digitalis.[96] Gubner and Acierno, on the basis of their experience with 2 fatalities encountered in treating digitalis toxicity, believe that quinidine is specifically contraindicated in this disorder,[97] and here the matter stands for the present.

*Assistant in medicine and Hochstetter Fellow, Department of Internal Medicine, University of Rochester School of Medicine and Dentistry; assistant resident, Strong Memorial Hospital, Rochester, New York.

The past two decades have also witnessed attempts to control these arrhythmias of digitalis origin with salts of various electrolytes. Ringer clearly demonstrated that normal cardiac contraction depended on the proper proportion of the different electrolytes in the perfusing medium; calcium promoted a more vigorous systole and potassium increased diastolic relaxation.[24, 25, 114] Subsequent investigation has confirmed the ability of the calcium salts to increase ventricular irritability[25, 27, 115] and cause characteristic changes in the electrocardiogram,[26, 27, 29, 30, 115, 116] which may be altered by potassium preparations.[117-119] The electrocardiographic manifestations of high and low levels of serum potassium are likewise well known.[30, 48, 115, 120-130] Cattell and Goodell interpreted the available data to imply that the action of the digitalis drugs might well be explained by an increase in the calcium-potassium ratio within the heart-muscle cell.[118] Recently Salter and Runels, in studies on the isolated frog heart, determined that there is an optimal concentration of potassium in the perfusing fluid above or below which contractility diminishes. They suggest that the traditional ratio of calcium to potassium does not directly reflect the fundamental mechanism of such ionic effects, which are best related using a nomogram involving both cations and digitalis.[131]

In the normal heart the content of potassium as well as of creatine and phosphorus is appreciably higher in the left than in the right ventricle.[13, 132] As heart weight increases beyond "normal limits" there is a progressive loss of potassium that is real and not a result of dilution by fat or edema fluid.[9-13, 132] In states of myocardial anoxia and insufficiency this loss of potassium is accentuated[1, 2, 9-13] and may be detected by an increase of potassium in the coronary sinus return[133] and in the serum potassium,[134-136] as well as by a negative potassium balance.[135, 136] In patients succumbing to right-sided heart failure of pulmonary origin, the right ventricular potassium content falls, while that of the left ventricle is unchanged; opposite effects are noted in fatal bouts of isolated left-sided heart failure, whereas if both chambers are involved the potassium content is uniformly decreased.[10]

There is much discussion concerning the role of digitalis in correcting the potassium losses associated with congestive heart failure. The digitalis drugs may sensitize the heart to acetylcholine and to vagal inhibition, two factors that may be associated

with a decrease in the intracellular concentration of this ion.[137] Several observers have reported a decrease in the potassium content of skeletal muscle[118] and cardiac muscle[138] exposed to therapeutic concentrations of digitalis preparations. Contrariwise, Calhoun and Harrison[139] and Wedd[140] could detect little change in the hearts of various laboratory animals that had been given adequate doses of digitalis, and still other investigators report increases in myocardial potassium in digitalized subjects.[141, 142] These last authors call attention to the sterol configuration of the glycosides and believe "that the effect of digitalis on heart muscle appears to be quite like that of the adrenal cortex hormone in that it acts to maintain the potassium within the cell."[142] The cardiac glycosides have been found to protect normal animals against potassium poisoning, to lower plasma potassium and to prolong life in adrenalectomized animals.[143]

There seems, however, to be general agreement that toxic doses of digitalis drive potassium from the heart muscle,[1, 138-141] possibly by depleting the energy-rich phosphate store.[1, 144] In isolated heart preparations digitalis can be enhanced or inhibited by appropriate variation of the potassium content of the perfusate.[131, 145] Complete absence of potassium accentuates the activity of the cardiac glycosides on the embryonic duck heart, for example.[145] Clinically, it has been appreciated that rapid loss of intracellular potassium in such conditions as diabetic acidosis,[73, 125, 127, 130, 146-148] chronic renal insufficiency,[130, 149, 150] intestinal disorders,[144, 151-155] metabolic alkalosis [144, 156] and myocardial infarction[133, 134, 157] may be associated with increased sensitivity to digitalis to the point of toxicity.[49] A similar heightened irritability may follow vigorous diuresis with mercurials,[39, 41, 44, 46, 49, 50, 135, 136, 158] the ion-exchange resins,[47-49] the artificial kidney[48, 49] and the adrenal and pituitary hormones[159, 160] or the use of glucose, insulin, ephedrine and adrenalin,[49, 119, 129, 161-163] all of which may be associated with a negative potassium balance.[49, 164] Merrill and his associates describe their experiences with a uremic patient with digitalis intoxication who was observed during a period of omission of the drug. The electrocardiographic abnormalities disappeared but could be reproduced, without additional digitalis, by lowering the serum potassium rapidly by means of the artificial kidney.[48] Similar effects were noted by Lown and his co-workers after depletion of body potassium by thiomerin, ammonium chloride and DOCA.[49]

It has, therefore, been thought that potassium might be able to inhibit the actions of digitalis on the heart by itself depressing cardiac irritability[165, 166] and by offsetting a specific loss of potassium from the heart that occurs whenever the latter is exposed to large or toxic amounts of digitalis. In 1930, Sampson and Anderson[167] were able to control five bouts of cardiac arrhythmias, including two of ventricular tachycardia, using 1 to 5 gm. of potassium orally. These same workers were later successful in abolishing ectopic rhythms in 50 per cent of a group of 58 patients, with similar doses of any of 6 salts of potassium in 25 per cent aqueous solution.[86] Among these were 2 cases of digitalis-induced ventricular premature beats. In most cases a definite response was noted within forty minutes and lasted from three to eight hours. Castleden succeeded in confirming the previous work of Sampson and Anderson by abolishing ventricular premature contractions in 4 patients with severe organic heart ailments, although doses of 6 gm. or over were necessary.[119] Others reported only "equivocal results" in the treatment of ventricular tachycardia, due in 50 per cent of cases to digitalis.[94] Sampson and his associates later induced ventricular ectopic beats with large amounts of digitalis in 13 of 33 patients with cardiovascular disorders. In contrast to their results in abolishing only 50 per cent of ectopic beats from other causes, they were able to terminate digitalis-induced extrasystoles in every case with 5 to 10 gm. of potassium acetate in 25 per cent solution[168]; therapy was accompanied by insignificant change in the serum-potassium concentration. It is of interest that in 1 patient there were "six to ten hour periods of relief from the visual symptom, flashes of light, of digitalis toxicity." Buff has reported the successful treatment of 18 cases of digitalis poisoning with 5-to-10-gm. doses of potassium chloride given in milk by Levine tube or, in 2 cases, by rectal instillation. After the acute toxic phase had subsided, these patients were started on 1-gm. doses of potassium chloride three times daily and one week later digoxin was resumed as well. Twenty-two other cases of congestive heart failure were treated from the beginning with digoxin and potassium chloride, and Buff reports that the co-operation and alertness of patients on this combination contrasts with the usual undesirable effects of digitalis and sodium restriction.[169] Enselberg and his associates became interested in the use of potassium salts after encountering digitalis poisoning in a fifty-eight-year-old woman recovering from diabetic acidosis in whom they successfully corrected the cardiac irregularity with a 2-gm. oral dose of potassium. They subsequently gave oral doses of potassium salts 40 times to 31 patients with a variety of arrhythmias and conduction disturbances. Definite effects were seen on each trial, appearing in thirty minutes and persisting for three to eight hours. In all of 24 cases ventricular extrasystoles were abolished or reduced. A patient with bidirectional ventricular tachycardia was managed successfully, and 2 patients with auricular tachycardia were reconverted to regular sinus rhythm. Auricular flutter and fibrillation were refractory to therapy, although there was marked slowing of the ventricular rate. In general, conduction disturbances be-

came more severe. No T-wave changes sufficient to be detected without careful measurement were noted. The effects were reproducible in each case with further doses of potassium.[73] Merrill[48] and Lown[49] were also able to reverse digitalis toxicity induced by various measures, using orally given potassium salts.

Although it is said to be "difficult if not impossible to produce potassium intoxication by the oral administration of potassium salts to patients with normal kidneys and circulation,"[170] toxic results have followed the oral use of potassium salts in doses as low as 2 to 8 gm. daily, with the production of auriculoventricular block, ventricular extrasystoles and auricular standstill.[123, 171] With larger doses, paresthesias appear.[172, 173] In the presence of oliguria or anuria such therapy may lead to the development of ectopic rhythms[124, 128, 130, 138] attributed to an escape of lower centers.[128] Sampson and Anderson reported the paradoxical development of ventricular premature beats, but their patients did not have digitalis poisoning.[86, 167] Most reports of the treatment of the digitalis disorders have concluded that the potassium salts are relatively nontoxic if given orally in doses of 2 to 10 gm. in the presence of normal renal function.[168, 169]

Magnesium salts are also known to depress the contractility of voluntary[174] and cardiac muscle.[175-178] This cardiac depression is not mediated by the vagus nerve, as it persists after vagotomy or atropinization,[84, 177] and is probably due to a direct myocardial action and possibly to a paralysis of cardioaccelerator ganglia.[179] Magnesium has little effect on the normal electrocardiogram.[179, 180]

In 1935 Zwillinger[99] reported a case in which syncope and ventricular flutter due to intravenously given strophanthin were treated successfully with an intracardiac injection of 10 cc. of a 15 per cent solution of magnesium sulfate. Similar results were noted in various other arrhythmias treated intravenously, and it was suggested that the magnesium salts might prove useful in combating digitalis poisoning. Magnesium was found to exert a protective action against toxic effects of digitalis in frogs, dogs and cats,[99, 180, 181] but other observers thought that heart block of digitalis origin might be increased and extrasystoles become more frequent.[176, 178]

Therapeutic trial with these magnesium preparations has shown rather favorable results. Zimdahl[182] described immediate termination of a bout of paroxysmal auricular tachycardia refractory to all other therapy, and Freundlich[96] was able to end a similar arrhythmia produced by digitalis on intravenous injection of 10 cc. of a 25 per cent solution of magnesium sulfate. Boyd and Scherf[183] reverted 6 of 10 cases of paroxysmal rapid heartbeat of auricular and ventricular origin with 15 to 20 cc. of the 20 per cent solution but were unsuccessful with lower concentrations. Although these authors were able to confirm the observation that digitalis-induced ventricular extrasystoles are abolished by magnesium, the transient effects and the prolongation of conduction time induced seemed to weigh against the use of the drug. Szekely[180] gave 20 cc. of a 20 per cent solution of magnesium sulfate intravenously to 26 patients with various arrhythmias. There seemed to be a greater effect on extrasystoles due to digitalis than on those from other causes. In 1 case the effect was lasting. Enselberg and his associates[184] treated 29 disorders of rhythm in 25 patients; in 13 cases digitalis intoxication was responsible. Only 1 patient with digitalis extrasystoles failed to respond. Sinus arrest was abruptly though transiently ended in one case. No striking effect was produced in a patient with prolonged auriculoventricular conduction. The effects were almost immediate in onset and rarely lasted for more than eight to ten minutes. In nearly all cases there was an initial cardiac acceleration followed by a somewhat slower rate before the effect was dissipated. Szekely and Wynne[84] terminated 2 paroxysms of bidirectional ventricular tachycardia and abolished 4 instances of extrasystoles with 15 to 20 cc. of a 20 per cent solution; the effects were lasting in all but 1 case.

The disadvantages of the use of magnesium are the transient action and the occasional tendency of the drug to increase the basic irregularity. The drug is rapidly excreted by the kidney, and little cumulation has been noted even after repeated prolonged injections.[185] There may also be a visible reddening of the blush areas of the body, accompanied by an unpleasant subjective sensation of intense heat.[180, 184]

Intravenously given procaine has been employed for some time by surgeons for the control of arrhythmias occurring during anesthetic procedures, but its use in clinical cardiology was limited by its central-nervous-system stimulation and its rapid degradation in the blood stream.[186] Diethylaminoethanol, one of the products of the hydrolysis of procaine, possesses its antiarrhythmic properties without its nervous-system stimulation.[187] A related compound, procaine amide (pronestyl), the amide analogue of procaine, has shown great promise in the treatment of digitalis-induced arrhythmias as well as those of other origin.

Procaine amide has been found to have a pronounced quinidine-like effect in both the isolated turtle heart and in man.[188, 189] In the turtle heart its chief effect is to raise the threshold for electrical stimulation, with a consequent lowering of ventricular conduction time. In contrast to quinidine, contractility is not depressed even with high concentrations; cardiac rhythm is unaltered, and there is no change in the effective refractory period.[189] Its effect on the auricular muscle has been stated to be one quarter that of quinidine.[188] Intravenous administration in man produces a decrease in car-

diac output, a slowing of pulmonary blood flow, with a drop in pulmonary arterial pressure, and variable changes in peripheral resistance.[190]

Stearns, Callahan and Ellis[191] reported that 13 of 14 patients with nodal or ventricular arrhythmias attributed to digitalis toxicity responded to doses of 60 to 800 mg. of procaine amide given intravenously. Supraventricular arrhythmias of other types were affected less strikingly. Berry and his associates[192] found the drug of value in terminating supraventricular as well as ventricular disturbances, although established flutter and fibrillation were refractory. Procaine amide effectively restored regular sinus rhythm in four of six episodes of ventricular tachycardia occurring in 5 patients who had been overdigitalized. McCord and Taguchi[193] were also able to demonstrate a pronounced effect of this drug, given intravenously, on the auricle, such as the suppression of premature auricular beats and the conversion of 6 to 16 instances of auricular fibrillation. Shack and his associates[194] restored normal sinus rhythm in all of 6 patients with auricular or nodal tachycardia and in 20 or 27 episodes of auricular fibrillation, using 4 to 6 gm. of procaine amide. Kayden and his co-workers[195, 196] suppressed ventricular ectopic beats in 54 patients with various types of heart disease; in many cases digitalis was responsible for the arrhythmia. After a single intravenous dose the effect occurred almost immediately and lasted for three to six hours — in some cases for more than twenty-four hours. The effect of an oral dose was usually delayed from thirty to sixty minutes, but the period of suppression was the same. In this same series, 13 of 15 patients with ventricular tachycardia reverted to regular sinus rhythm under procaine-amide treatment; 6 had been refractory to quinidine. In 2 of these patients the onset of ventricular tachycardia was related to the use of the digitalis preparations. In 1 patient four bouts of tachycardia had been precipitated by the glycosides, and in every case procaine amide, given intravenously or orally or by both routes, ended the disturbance. Chronic auricular arrhythmias in 24 patients did not respond. Schaffer and his associates reported success in 1 patient and failure in another who had auricular arrhythmias of digitalis origin.[197]

Kinsman and his associates report similar successes with ventricular arrhythmias and inconstant results with auricular disorders.[198, 199] Anderson and his colleagues were able to restore regular sinus rhythm using intravenous procaine amide in a patient in whom trigeminy, bigeminy and ventricular tachycardia appeared after the use of digitalis.[200]

Procaine amide is rapidly and completely absorbed from the gastrointestinal tract, and peak concentration in the blood is reached between one and two hours after its oral administration.[196] Excretion is slow, plasma levels declining about 15 per cent per hour; about 60 per cent is excreted unchanged in the urine.[195-197] Repeated oral doses produce a relative plateau after thirty-six to forty-eight hours.[195-197] The intravenous route is urged only for critically ill patients or those unable to take oral medications.[191-197] The rate of intravenous administration should not exceed 100 to 200 mg. per minute for a total of 1 gm.[192, 196] Oral dosage may be as high as 1.25 gm. initially, followed by a second dose of 0.75 gm. within one hour and succeeding doses of 0.5 to 1.0 gm. every two hours, if there is no appreciable change. It may be necessary to continue oral maintenance therapy with doses of from 0.5 to 1.0 gm. every three to six hours; smaller doses may be equally effective in the presence of impaired renal function.[195, 196] Several patients have received procaine amide continually for as long as nine months, the majority without apparent harmful effects[195]; toxic manifestations have been noted, however.

Major toxic effects have been largely limited to the cardiovascular and gastrointestinal systems. Anorexia, nausea and vomiting were observed only with high oral dosage.[191-196] Electrocardiographic changes may be observed with either oral or intravenous therapy in about one third of patients and consist of widening of the QRS and QT intervals, diminution in voltage of the ventricular complexes and inconstant changes of ST segments and T waves.[191-196] The PR interval may be widened in some cases.[189,193] More serious toxic effects appear with bouts of ventricular tachycardia, bundle-branch block and electrical pulsus alternans,[189] seen especially in elderly patients with advanced cardiac failure who are treated by the intravenous route. A single death has followed what may have been a too-rapid injection in a patient with extensive coronary-artery disease.[196] Hypotension has been noted in about one third of the patients who had tachycardia (which might have been held responsible); although it may follow as little as 70 mg. given intravenously, it has rarely been observed with oral therapy.[190-197] Neosynephrine may counteract this fall in blood pressure.[191] Cerebrovascular effects may take the form of headache, drowsiness or, more rarely, convulsions or frankly psychotic behavior, all of which subside rapidly after withdrawal of the drug.[192, 200] Urticaria has been noted on occasion,[192] and granulocytopenia and even agranulocytosis have occurred in a very few of the patients maintained on pronestyl over long periods of time.[201]

Summary

The indications for the use of digitalis, as well as the contraindications to its employment, have been discussed.

Digitalis toxicity may occur when the drug is given without adequate indication; if vigorous diuresis causes a specific intracellular deficit of potassium; if the drug is administered without ap-

preciation of the wide variation in biologic potency of the many preparations available; if characteristic signs and symptoms of toxicity do not appear or are obscured by concomitant disease; with relative ease in the severer grades of heart failure or in the presence of certain of the arrhythmias.

Digitalis may produce every known type of arrhythmia and conduction disorder. The onset of a rapid regular heart rate under digitalis therapy may represent the development of paroxysmal auricular, nodal or ventricular tachycardia.

Development of any of the clinical or electrocardiographic evidences of digitalis poisoning should indicate immediate withdrawal of the drug. In addition, certain positive measures may be employed to regulate the rhythm before irreversible damage is produced.

The potassium salts, given orally, are particularly useful in the control of ventricular arrhythmias of digitalis origin and are without danger in the presence of normal renal function.

Magnesium sulfate, given intravenously, may also be useful in the ventricular disorders, but its transient effects, unpleasant side-actions and occasional paradoxical activity should limit its use to refractory arrhythmias.

Procaine amide is also effective in the treatment of the ventricular arrhythmias as well as of auricular disorders of recent origin. Its intravenous administration should be reserved for critically ill patients who cannot take oral medication. Both forms of procaine amide have a prolonged effect; thus its use is feasible in long-term therapy. Nearly all its serious toxic effects have followed intravenous use. Procaine amide may be particularly useful when renal function is impaired and use of the potassium salts is contraindicated.

The author wishes to express his appreciation of the encouragement and helpful criticism of Dr. William S. McCann.

References

113. Nielsen, N. A. and Trier, M. Comparison of changes in human electrocardiogram following administration of strophanthin, acetylcholine and during vagal stimulation. *Am. Heart J.* **17**:515-523, 1939.
114. Ringer, S. Concerning influence exerted by each of constituents of blood on contraction of ventricle. *J. Physiol.* **3**:380-393, 1882.
115. Hoff, H. E., Smith, P. K., and Winkler, A. W. Electrocardiographic changes and concentration of calcium in serum following intravenous injection of calcium chloride. *Am. J. Physiol.* **125**:162-171, 1939.
116. Langendorf, R., and Pirani, C. L. Heart in uremia: electrocardiographic and pathologic study. *Am. Heart J.* **33**:282-307, 1947.
117. Wiggers, C. J., Theisen, H., and Shaw, H. D. B. Studies on ventricular fibrillation produced by electric shock: action of antagonistic salts. *Am. J. Physiol.* **93**:197-212, 1930.
118. Cattell, M., and Goodel, H. On mechanism of action of digitalis glucosides on muscle. *Science* **86**:106, 1937.
119. Castleden, L. I. M. Effect of potassium salts on cardiac irregularities. *Brit. M. J.* **1**:7-9, 1941.
120. McLean, F. C., Bay, E. B., and Hastings, A. B. Electrical changes in isolated heart of rabbit following changes in potassium content of perfusing fluid. *Am. J. Physiol.* **105**:72, 1933.
121. Winkler, A. W., Hoff, H. E., and Smith, P.K. Electrocardiographic changes and concentration of potassium in serum following intravenous injection of potassium chloride. *Am. J. Physiol.* **124**:478-483, 1938.
122. Thomson, W. A. R. Potassium and T-wave of electrocardiogram. *Lancet* **1**: 808-811, 1939.
123. Stewart, H. J., Shepard, E. M., and Horger, E. L. Electrocardiographic manifestations of potassium intoxication. *Am. J. Med.* **5**: 821-827, 1948.
124. Tarail, R. Relation of abnormalities in concentration of serum potassium to electrocardiographic disturbances. *Am. J. Med.* **5**:828-837, 1948.
125. Nadler, C. S., Bellet, S., and Lanning, M. Influence of serum potassium and other electrolytes on electrocardiogram in diabetic acidosis. *Am. J. Med.* **5**:838-848, 1948.
126. Currens, J. H., and Crawford, J. D. Electrocardiogram and disturbance of potassium metabolism. *New Eng. J. Med.* **243**:843-850, 1950.
127. Bellet, S., et al. Electrocardiograph patterns in hypopotassemia: observations on 70 patients. *Am. J. M. Sc.* **219**:542-558, 1950.
128. Levine, H. D., Merrill, J. P., and Somerville, W. Advanced disturbances of cardiac mechanism in potassium intoxication in man. *Circulation* **3**:889-905, 1951.
129. Parrish, A. E., Sugar, S. J., and Fazekas, J. F. Relation between hypoglycemia, hypokalemia and electrocardiographic changes in non-diabetic patients. *Proc. Nat. Meet. Am. Fed. Clin. Res.* May, 1951. (Abstr.)
130. Danowski, T. S Newer concepts of role of potassium in disease. *Am. J. Med.* **7**:525-531, 1949.
131. Salter, W. T., and Runels, E. A. Nomogram for cardiac contractility involving calcium, potassium and digitalis-like drugs. *Am. J. Physiol.* **165**:520-526, 1951.
132. Wilkins, W. E., and Cullen, G. E. Electrolytes in human tissues: comparison of normal hearts with hearts showing congestive heart failure. *J. Clin. Investigation* **12**:1063-1074, 1933.
133. Dennis, J., and Moore, R. Potassium changes in functioning heart under conditions of ischemia and of congestion. *Am. J. Physiol.* **123**:443-447, 1938.
134. Wilhelm, S. K. Alterations in serum potassium and sodium in acute myocardial infarction. *Am. J. Clin. Path.* **21**:146-148, 1951.
135. Uhl, H. M. S., et al. Fluid and electrolyte balance during recovery from high output failure due to beri-beri. *Proc. Nat. Meet. Am. Fed. Clin. Res.* May, 1951. (Abstr.)
136. McCaughey, R. S., et al. Plasma sodium and potassium concentrations in congestive heart failure. *Proc. Nat. Meet. Am. Fed. Clin. Res.* May, 1951. (Abstr.)
137. Howell, W. H. Vagus inhibition of heart in its relation to inorganic salts of blood. *Am. J. Physiol.* **15**:280-294, 1905.
138. Wood, E. H., and Moe, G. K. Electrolyte and water content of ventricular musculature of heart-lung preparation with special reference to effects of cardiac glycosides. *Am. J. Physiol.* **136**:515-522, 1942.
139. Calhoun, J. A., and Harrison, T. R. Studies in congestive heart failure: effect of digitalis on potassium content of cardiac muscle of dogs. *J. Clin. Investigation* **10**:139-144, 1931.
140. Wedd, A. M. Influence of digoxin on potassium content of heart muscle. *J. Pharmacol. & Exper. Therap.* **65**:268-274, 1939.
141. Hagen, P. S. Effects of digilanid C in varying dosage upon potassium and water content of rabbit heart muscle. *J. Pharmacol. & Exper. Therap.* **67**:50-55, 1939.
142. Boyer, P. K., and Poindexter, C. A. Influence of digitalis on electrolyte and water balance of heart muscle. *Am. Heart J.* **20**:586-591, 1940.
143. Zwemer, R. L., and Lowenstein, B. E. Cortin-like effects of steroid glycosides on potassium. *Science* **91**:75, 1940.
144. Wollenberger, A. Effect of ouabain and digoxin on energy-rich phosphate store of heart. *Federation Proc.* **7**:266, 1948.
145. Friedman, M., and Bine, R., Jr. Observations concerning influence of potassium upon actions of a digitalis glycoside (lanatoside C). *Am. J. M. Sc.* **214**:633-638, 1947.
146. Holler, J. W. Potassium deficiency occurring during treatment of diabetic acidosis. *J. A. M. A.* **131**:1186-1189, 1946.
147. Frenkel, M., Groen, J., and Willebrands, A. F. Low serum potassium level during recovery from diabetic coma: with special reference to its cardiovascular manifestations. *Arch. Int. Med.* **80**: 728-738, 1947.
148. Nadler, C. S., Bellet, S., Gazes, P. C., and Steiger, W. A. Administration of potassium to patients with prolonged vomiting and diabetic acidosis. *J. Lab. & Clin. Med.* **35**:842-853, 1950.
149. Tarail, R., and Elkinton, J. R. Potassium deficiency and role of vomiting in its production. *J. Clin. Investigation* **28**: 99, 1949.
150. Elkinton, J. R., Squires, R. D., and Singer, R. B. Intracellular cation exchanges in acidosis and renal insufficiency. Effects of alkali therapy. *J. Clin. Investigation* **30**:381-387, 1951.
151. Darrow, D. C. Body fluid physiology: relation of tissue composition to problems of water and electrolyte balance. *New Eng. J. Med.* **233**:91, 1945.
152. Bellet, S., Nadler, C. S., Gazes, P. C., and Lanning, M. Effect of vomiting due to intestinal obstruction on serum potassium: chemical and electrocardiographic observations in fifteen cases: preliminary report. *Am. J. Med.* **6**:712, 1949.
153. Randall, H. T., Habif, D. V., Lockwood, J. S., and Werner, S. C. Potassium deficiency in surgical patients. *Surgery* **26**:341-363, 1949.
154. Evans, I. E. Potassium deficiency in surgical patients: its recognition and management. *Ann. Surg.* **131**:945, 1950.
155. Nelson, R. M., Friesen, S. R., and Kremen, A. J. Refractory alkalosis and potassium ion in surgical patients. *Surgery* **27**:26-40, 1950.
156. Darrow, D. C., Schwartz, R., Ianucci, J. F., and Coville, F. Relation of serum bicarbonate concentration to muscle composition. *J. Clin. Investigation* **27**:198-208, 1948.
157. Herrmann, G., and Erhard, P. Total creatinine, phosphates, calcium and potassium in normal and infarcted myocardium of dog. *Proc. Soc. Exper. Biol. & Med.* **38**:35-37, 1938.
158. Blumgart, H. L., et al. Action of diuretic drugs: action of diuretics in normal persons. *Arch. Int. Med.* **54**:40-81, 1934.
159. Campbell, C. G., and Friedman, S. M. Effect of potassium and DOCA in acute heart injury in rat. *Circulation:* **2**:230, 1950.

160. Seldin, D. W., Welt, L. G., and Cort, J. Effect of pituitary and adrenal hormones on metabolism and excretion of potassium. *J. Clin. Investigation* **30**: 673, 1951.

161. Fenn, W. Deposition of potassium and phosphate with glycogen in rat livers. *J. Biol. Chem.* **128**:297-307, 1939.

162. Gass, H., Cherkasky, M., and Savitzky, N. Potassium and periodic paralysis: metabolic study and physiological considerations. *Medicine* **27**:105-137, 1948.

163. Danowski, T. S., Elkinton, J. R., Burrows, B. A., and Winkler, A. W. Exchanges of sodium and potassium in familial periodic paralysis. *J. Clin. Investigation* **27**:65-73, 1948.

164. Hoffman, W. S. Clinical physiology of potassium. *J. A. M. A.* **144**:1157-1162, 1950.

165. Stempien, S. J., and Katz, K. H. Quinidine and potassium in treatment of refractory paroxysmal ventricular tachycardia. *Am. Heart J.* **24**: 555-558, 1942.

166. Schlachman, M., and Rosenberg, B. Effect of potassium on inverted T waves in organic heart disease. *Am. Heart J.* **40**: 81-92, 1950.

167. Sampson, J. J., and Anderson, E. M. Therapeutic use of potassium in certain cardiac arrhythmias. *Proc. Soc. Exper. Biol. & Med.* **28**:163, 1930.

168. Sampson, J. J., Albertson, E. C., and Kondo, B. Effect on man of potassium administration in relation to digitalis glycosides, with special reference to blood serum potassium, electrocardiogram, and ectopic beats. *Am. Heart J.* **26**:164-179, 1943.

169. Buff, I. E. Use of potassium chloride and digoxin in congestive heart failure. *South. M. J.* **42**: 1037-1040, 1949.

170. Darrow, D. C., and Pratt, E. L. Fluid therapy: relation to tissue composition and expenditure of water and electrolyte. *J. A. M. A.* **143**:365-372 and 432-439, 1950.

171. Stewart, H. J., and Smith, J. J. Changes in electrocardiogram and in cardiac rhythm during therapeutic use of potassium salts. *Am. J. M. Sc.* **191**:177-197, 1941.

172. Keith, N. M., Osterburg, A., and Burchell, H. B. Some effects of potassium salts in man. *Ann. Int. Med.* **16**:879-892, 1942.

173. Engel, F. L., Martin, S. P., and Taylor, H. On relation of potassium to neurological manifestations of hypocalcemic tetany. *Bull. Johns Hopkins Hosp.* **84**:285-301, 1949.

174. Jolyet, F., and Cahours. Sur l'action physiologique des sulfates de potasse, de soude et de magnésie en injection dans le sang. *Arch. de Physiol.* **2**:113-120, 1869.

175. Miller, J. R., and Van Dellen, T. R. Electrocardiographic changes following intravenous administration of magnesium sulfate: experimental study on dogs. *J. Lab. & Clin. Med.* **23**:914-918, 1938.

176. Smith, P. K., Winkler, A. W., and Hoff, H. E. Electrocardiographic changes and concentration of magnesium in serum following intravenous injection of magnesium salts. *Am. J. Physiol.* **126**:720-730, 1939.

177. Van Dellen, T. R., and Miller, J. R. Electrocardiographic changes following intravenous administration of magnesium sulfate. Experimental study on dogs. *J. Lab. & Clin. Med.* **24**:840-843, 1939.

178. Miller, J. R., and Van Dellen, T. R. Electrocardiographic changes following intravenous administration of magnesium sulfate. Combined effect with digitalis. *J. Lab. & Clin. Med.* **26**:1116-1120, 1941.

179. Bernstein, M., and Simkins, S. Magnesium: effects of intravenous injection on the human heart. *J. Lab. & Clin. Med.* **25**:131-141, 1939.

180. Szekely, P. Action of magnesium on heart. *Brit. Heart J.* **8**:115-121, 1946.

181. Rothberger, C. J., and Zwillinger, L. Über die Wirkung von Magnesium auf die Strophanthin- und die Barium-Tachykardie. *Arch. f. exper. Path. u. Pharmakol.* **181**: 301-316, 1936.

182. Zimdahl, W. T. Magnesium sulfate in paroxysmal tachycardia. *Ann. Int. Med.* **25**:531-533, 1946.

183. Boyd, L. J., and Scherf, D. Magnesium sulfate in paroxysmal tachycardia. *Am. J. M. Sc.* **206**:43-48, 1943.

184. Enselberg, C. D., Simmons, H. G., and Mintz, A. A. Effects of magnesium upon cardiac arrhythmias. *Am. Heart J.* **39**:703-712, 1950.

185. McCance, R. A., and Widdowson, E. M. Fate of calcium and magnesium after intravenous administration to normal persons. *Biochem. J.* **33**:523-529, 1939.

186. Burstein, C. L. Utility of intravenous procaine in anesthetic management of cardiac disturbances. *Anesthesiology* **10**:133-144, 1946.

187. Rosenberg, B., et al. Studies on diethylaminoethanol: physiological disposition and action on cardiac arrhythmias. *J. Pharmacol. & Exper. Therap.* **95**:18-27, 1949.

188. Newman, P. J., and Clark, B. B. Comparative study of pharmacological properties of procaine and procaine amide. *Federation Proc.* **9**:304, 1950.

189. Wedd, A. M., Blair, H. A., and Warner, R. S. Action of procaine-amide on heart. *Am. Heart J.* **42**:399-405, 1951.

190. McClendon, R. L., Hansen, W. R., and Kinsman, J. M. Hemodynamic changes following procaine amide administered intravenously. *Am. J. M. Sc.* **222**:375-381, 1951.

191. Stearns, N. S., Callahan, E. J., and Ellis, L. B. Clinical study of intravenous procaine-amide (pronestyl): its value and hazards. *J. Clin. Investigation* **30**:676, 1951.

192. Berry, K., et al. Use of pronestyl in treatment of ectopic rhythms: treatment of 98 episodes in 78 patients. *Am. J. Med.* **11**:431-441, 1951.

193. McCord, M., and Taguchi, J. T. Study of effect of procaine amide hydrochloride in supraventricular arrhythmias. *Circulation* **4**:387-393, 1951.

194. Shack, J. A., Hoffman I., and Vessell, H. Response of arrhythmias and tachycardias of supraventricular origin to procaine-amide. *Scientific Sessions Am. Heart A.* June, 1951. (Abstr.)

195. Kayden, H. J., Brodie, B. B., and Steele, J. M. Use of procaine amide in cardiac arrhythmias. *Mod. Conc. Cardiovasc. Dis.* **20**: 100, 1951.

196. Kayden, H. J., et al. Use of procaine amide in cardiac arrhythmias. *Circulation* **4**:13-22, 1951.

197. Schaffer, A. I., et al. Procaine-amide: effect on auricular arrhythmias. *Am. Heart J.* **42**:115-123, 1951.

198. Kinsman, J. M., et al. Procaine-amide (pronestyl) in treatment of disorders of cardiac rhythm. *Kentucky M. J.* **48**:509, 1950.

199. Kinsman, J. M., Hansen, W. R., and McClendon, R. L. Procaine-amide (pronestyl) in treatment of cardiac arrhythmias. *Am. J. M. Sc.* **222**:365-374, 1951.

200. Anderson, R. M., Boone, J. A., and Coleman, R. R. Use of procaine amide in ventricular tachycardia. *South. M. J.* **44**:905-909, 1951.

201. Inouye, M., Millar, J., and Townsend, J. H. Agranulocytosis following maintenance dosage of pronestyl: report of severe case with recovery. *J. A. M. A.* **147**:652, 1951.

MEDICAL INTELLIGENCE

MEDICAL WRITING AS OBSERVED BY A READER*

ROGER I. LEE, M.D.

BOSTON

IT is my privilege to have been intimately acquainted with medical literature for these many years, as both a consistent reader and a not infrequent contributor. Having devoted my attention largely to the original articles, not only in my own field of interest but also in other fields, in the hope of finding out something about the weather on various fronts, I have never had any lasting theories in regard to editorials, reviews of books and articles or special features.

The special journals have interested me less and less, for many of the articles contained in them seem unduly long, prolix and overdevoted to the jargon of the specialty. One is painfully reminded at times of a cynical review of one of Henry James' novels: "How Mary Smith stepped on Ann Brown's dress and nothing happened in several hundred pages."

My fate has been such that I have had to listen for many weary hours to the feud between the late Dr. William S. Thayer of Baltimore and the recent editor of the *Journal of the American Medical Association*, Dr. Fishbein, in regard to the prevalent editorial practice of altering copy — such as changing *pathological* to *pathologic*, for instance.

I have my own prejudices on somewhat different lines; for example, I dislike a string of names as co-authors. When I see an additional string of names to whom the authors are indebted in varying degree, I wonder who did the work and wrote the paper anyway. Is this supposed to add to each person's bibliography and impress the election committee of the select medical societies or the arbiters of the fund that assisted financially in the work reported? Too often there is a touch of the old Teutonic technic, in which the head of a department or clinic had his name on all articles issuing therefrom. — Yes, it happens also in the U. S. A.

My minor prejudices, such as those in favor of clear and understandable English and an honest bibliography with verified references, we may pass over.

Sir William Osler may be said to have set the pattern of medical writing for the last two or three generations. After a discussion of the history, there came always the section on pathology, which later included bacteriology and would in modern days include also physiology and chemistry, or perhaps physics. There then followed a discussion of symptomatology, diagnosis, differential diagnosis and treatment. Osler's really great contribution to medical writing, in addition to and apart from his impeccable style, was his attempt to correlate the clinical and the pathological findings. Although he was not a master of statistics, he avoided with considerable skill the usual pitfalls attending their use. He put an end, I believe, to the old routine of classifying any disease into mild, moderately severe and very severe cases. I have been spared for years the reading or hearing of such a classification. The date of its death was just prior to that of the once familiar "When I was in Vienna —" or "when I worked in Vienna"!

To be sure, one may read in a modern text, although never in Osler, such a crime against logic as the statement that pernicious or Addisonian anemia is always controlled by the administration of liver — and also that the administration of liver is an absolute therapeutic diagnostic test of pernicious anemia. Of course, neither of these two statements is true, and it should not require a professor of logic to point that out. Deductions from given data are often far from simple — but not so in much medical writing!

It happens that much important information, such as that concerning the value of antibiotics, depends largely on deductions from data, yet all the sins of medical writing may be found here.

Are three cases enough to make a series? Parenthetically, I have a fondness for the carefully reported *single* case, which, in the days before mass production, often was a feature of a medical journal. But a series of three cases leads to statistical atrocities and aberrations in deductions.

The papers that have been published in reputable medical journals on the subject of any single antibiotic are for the most part pretty terrible. I am reasonably certain that the heads of pharmaceutical houses must experience a feeling of satisfaction on seeing how the articles of medical men in the medical press often take on the flavor of advertisements for commercial nostrums. I am referring mainly to the lack of critical judgment that is shown, — particularly in the use of statistical data, — and the absence of logical deductions.

Of course, the antibiotics represent a new epoch in the medical mastery of infectious diseases, the lessening of mortality and the prolongation of human life. However, I should like to see a more discriminating attitude in the reporting of observations on their use. Few medical writers can attain a so-called popular style and popular appeal and still pay due homage to scientific accuracy; perhaps it is as well.

*Presented at a meeting of the State Medical Journal Conference, Chicago, November 12 and 13, 1951.

Your cynic may well query: What has become of pneumonia, the friend of the aged? — and the non-golfer may chuckle at George Bernard Shaw, always an arresting cynic, who referred to golf as needlessly prolonging the lives of useless men. This does not mean that pneumonia should be encouraged or that golf is an undesirable game; it is just another point of view. Some patients used to recover from pneumonia in the days before antibiotics, some persons have never played golf and some survive tonsillitis without antibiotic therapy. A cold is still a cold, even if it is caused by a virus. And I blush whenever I think of the situation based on medical writing in regard to brucellosis.

And where today are those patients with intractable anginal pain, whose counterparts were operated on not so long ago? What has happened to the operation and what has happened to the pain? No one, I submit, would ever admit that the pain was exaggerated by the doctors, even if by the patient. And yet there seems to have been some lack of objectivity — entirely involuntary, perhaps.

It is precisely this failure of critical scrutiny and balanced judgment to which I refer. I believe that this has had a profound and deleterious effect on medical practice. I believe it is a trend toward careless, casual and generally optimistic thinking and writing that is perhaps a phase of present-day life.

I pose the question, which I cannot answer: "Are the younger medical men as interested in their medical journals as they should be? If not, does the fault lie in the men or in the journals?" As I have said, I do not know the answer. I am inclined to think that medical men have so many meetings and opportunities for discussion that the written word does not carry the weight that it once did. I am inclined to think also that this has led to informality, casualness and carelessness in writing. I think, too, that multiple authorship and a sort of mass production of papers, — possibly to acquire a considerable bibliography, — contribute to this end.

The other day, in looking over the laboratory manual of a certain hospital, I found a well known technic referred to, listed as quoted by Blank. The reference given was to Blank. This particular technic, which is still unchanged, was developed in that very hospital. Why was the original report not cited?

If I sound disgruntled, it is not my intent. I should like to see changes in medical writing that would make the text more exact — but not more pedantic. I believe much more care should be taken in regard to the statistical data and the logical deductions from all the evidence. I hope for a calm, cold critical judgment.

The argument about the written and the spoken word has gone on since the advent of printing. The ordinary lecture as a means of education perhaps reached a peak in the days of the Chautauqua. Gradually visual aids were introduced, such as lantern slides, live clinics with patients, ward rounds, public operations and laboratory demonstrations. Now we have television and radio. To be sure, the technic is not perfect, as when the lantern slides contain so much data in such fine print that the audience cannot read them, or when the lecturer moves away from the microphone, turns his back on the audience, talks to the lantern slide and is entirely inaudible.

In the meantime, the printed word has come often to be accompanied by charts and illustrations, which, incidentally, are very expensive.

On the other hand, the printed word has permanence. The material should be source material. It should be susceptible of ready reference. And may I here be permitted an aside to condemn with great vehemence those writers who pick titles that do not reflect accurately the subject matter of their papers? How can references like those be catalogued and indexed?

It is certainly very pleasant to go to medical meetings, especially if one has an opportunity to pick over the brains of the speaker in a quiet corner and to learn thereby whether or not to put his articles and talks in the "must" or "never again" categories. It is not always possible to form such an opinion of a man's personality from the written word. But this may be debated.

As an educational technic, I believe that the modern trend is away from the printed word and toward the spoken word. I think the various visual aids are being more widely utilized — and perhaps they are better fitted than the written word to assist and enlarge on the spoken word.

To my mind this is an unfortunate trend — even admitting that it is probably easier for those both on the platform and in front of it. But I insist that the printed word is the foundation and backbone of education and the search for truth. In my opinion our medical writings in our medical journals are precious and priceless bulwarks of medical education, especially at the postgraduate level. One finds permanence and an opportunity for reference. I submit, moreover, that one should find a precision, a judgment and a finality that are not necessarily so characteristic of the spoken word. I also believe that of late the printed word has acquired some of the casualness and carelessness of the spoken word, which is unfortunate.

Medicine moves at such a pace that the printed word in books belongs almost to another and earlier generation before it reaches its public. But what I have tried to describe is the place and function of the printed word in our medical journals.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 38071

PRESENTATION OF CASE

A sixty-one-year-old woman was admitted to the hospital because of weight loss and shortness of breath.

Three months prior to entry the patient first noted a dry cough productive of small amounts of whitish sputum, which on one occasion was blood tinged, shortness of breath on exertion, weakness and easy fatigability. On moderate exertion such as climbing the three flights of stairs to her home the patient developed marked dyspnea and a "sickly feeling" in the epigastrium. Roentgenograms showed diffuse nodular mottling of both lung fields (Fig. 1). The symptoms were slowly progressive, and in addition she developed marked anorexia and lost 20 pounds in weight. For one month prior to admission she had a "heavy sensation" in the epigastrium following meals that lasted about one-half hour and was not associated with nausea or vomiting. For the three weeks before admission she had had occasional twinges of sharp pain beneath the right breast, radiating into the right axilla. There had been no chills, night sweats, orthopnea, urinary symptoms or change in bowel habits. By the time of admission she had become so weak that she was no longer able to do her own housework.

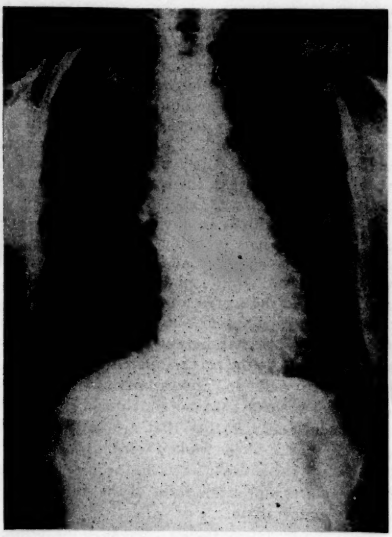

FIGURE 1. *Roentgenogram Taken Two and a Half Months Before Admission.*

Physical examination revealed a somewhat thin woman, lying flat in bed. The respirations were rapid and shallow, with a prolonged expiratory phase. The neck veins were flat. The anteroposterior diameter of the chest was increased. Coarse rhonchi were heard in the right axilla, and less constant wheezes were heard throughout the chest. Examination of the heart, abdomen, pelvis and extremities was negative.

The temperature was 99°F., the pulse 84 and the respirations 26. The blood pressure was 125 systolic, 75 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 16.8 gm., a white-cell count of 9600, with 81 per cent neutrophils, a red-cell count of 5,000,000 and a hematocrit of 49. The nonprotein nitrogen was 20 mg., the total protein 6.75 gm., with an albumin-globulin ratio of 1.4, the serum calcium 10.2 mg., the phosphorus 3.5 mg., the alkaline phosphatase 12.6 units and the total bilirubin 1.2 mg. per 100 cc. The bromsulfalein excretion showed 23 per cent retention, the cephalin flocculation was ++ in forty-eight hours and the prothrombin time was normal. A stool examination was guaiac negative. A tuberculin test was negative in 1:1000 dilution. The vital capacity was 2080 cc. Smears of the sputum, which was scanty, showed an occasional chain of gram-positive cocci, a few leukocytes, many epithelial cells and no acid-fast organisms. Chest roentgenograms revealed diffuse nodular densities throughout both lung fields with some confluence of the patches (Fig. 2). A gastrointestinal series and metastatic bone series were negative. Bronchoscopic examination showed findings consistent with chronic bronchitis; cytologic examination of the bronchial washings from the right main bronchus was doubtful for malignant cells.

There was little change in the condition until the eleventh hospital day, when the patient developed a temperature of 103°F., increased dyspnea, cough, cyanosis and pleuritic-type right-chest pain. In addition to the wheezes previously heard in the

chest there were numerous fine moist inspiratory rales in the lower third of the right lung. There was temporary improvement with Chloromycetin therapy, although she was still acutely ill; she was slightly cyanotic even with oxygen therapy and definitely dyspneic without it. Over a period of forty-eight hours she became totally unresponsive and had rapid gasping respirations; chest roentgenograms at this time suggested a slight increase in the areas of confluent density; the carbon dioxide was

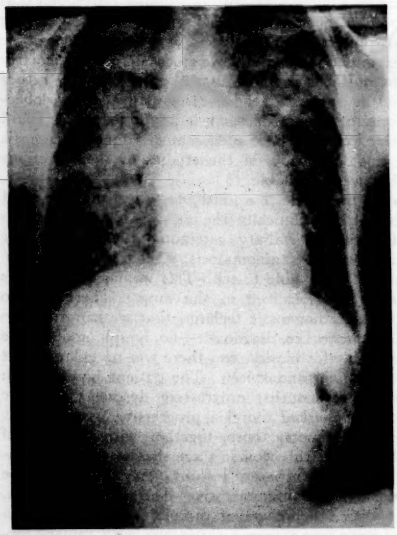

FIGURE 2. *Roentgenogram Taken During Admission.*

38 milliequiv. per liter and the pH 7.18. She died on the twenty-third day, approximately forty-eight hours after the onset of unconsciousness.

DIFFERENTIAL DIAGNOSIS

DR. THEODORE L. BADGER*: I wonder if you would show the x-ray films now.

DR. JOSEPH HANELIN: These films extend over a three-month period. I presume the first one was made shortly after the patient was seen in the Out Patient Department and the last one shortly before death (Fig. 1 and 2). Both lungs are diffusely involved by small nodular lesions, varying in size up to 4 to 5 inches in diameter. In successive films it is obvious that there is progressive growth and confluence of these lesions to form larger homogeneous zones of density.

DR. BADGER: This woman had apparently been quite well until three months before admission, when the shortness of breath was the first complaint, followed in succession by weakness, considerable loss of weight, marked anorexia and finally a rather sudden death. I think we are dealing with an extracardiac problem and that the mechanism of circulation played little or no role as far as the dyspnea was concerned. The patient had never been orthopneic; I think that alone takes her out of the cardiac group and puts her into the category of dyspnea of primarily pulmonary origin.

The problem revolves around the bilaterally symmetrical nature of this miliary type of lesion, described as miliary simply because it was in the form of nodules that over a period of time had become more confluent but had not actually shown any striking change. Time does not permit me to review the many varieties of miliary disease of the lung, but there are a few of which I would like to speak in an effort to differentiate the possibilities that I see in this particular case.

First of all, in any miliary lesion of the lung one has to think of miliary tuberculosis; I am forced to consider that as a primary possibility, as it is perhaps the most common of all. In this age group miliary tuberculosis is perhaps less common. I assume that during her hospital stay she was quite afebrile; she ran a relatively normal temperature, — occasionally up to 99°F., — had a relatively slow pulse, had somewhat elevated respirations and was never really seriously toxic from some overwhelming infection, although she was short of breath and weak. Miliary tuberculosis may occur in persons of this age but not with great frequency; very rarely it is in the lungs only and not in some other organ — spleen, liver or lymph nodes. I am unable to see anything I can really describe as enlargement of hilar lymph nodes. I am inclined to believe that this was not miliary tuberculosis because of the absence of toxicity and its failure to appear in other parts of the body. The tuberculin test, — negative at 1:1000, — is not an accurate reflection of whether this was or was not tuberculosis; if tuberculosis should be overwhelming the test might well be negative down through 1 mg. of O.T.

One of the conditions more commonly confused with miliary tuberculosis is, of course, sarcoidosis, which may appear in a miliary form such as this but not usually with the associated constitutional symptoms that this patient developed. The more acute forms of sarcoidosis primarily involving the lungs do not usually advance as rapidly as this, although we now see occasional cases of early sarcoidosis that run a more rapid course; it is miliary in type, does produce rather severe constitutional symptoms and may show temporary response to Chloromycetin or other antimicrobic therapy. It is a rather unusual

*Assistant visiting physician, Boston City Hospital.

occurrence, however, in this age group. I have never seen it in this particular form in patients past sixty. Usually sarcoidosis is a roentgenologic surprise, with lesions out of all proportion to the constitutional symptoms. It commonly involves the lymphatic system and is accompanied by enlargement either of hilar lymph nodes or of the lymph nodes elsewhere, as well as enlargement of the spleen and liver. This case had none of these things. I am not inclined to put a great deal of emphasis on sarcoidosis; I think the progress was too rapidly progressive.

It seems unlikely that it was one of the more benign varieties of miliary disease associated with an occupational hazard — which the patient apparently did not have. There are, however, other varieties of granulomatous disease of the lungs, the etiology of which is completely unknown, that may progress as rapidly as this one had progressed; these occur usually in the younger age group, cause considerable replacement of pulmonary tissue, are limited primarily to the lungs and, as a matter of fact, in recent years have been found to respond to cortisone and adrenocorticotropic therapy. There is no possible chance of making this diagnosis except by biopsy of lung tissue itself.

I think it worth while to mention Loeffler's syndrome, one of the allergic diseases of the lung; Nemir[1] has reported three cases of Loeffler's syndrome, in miliary form, with a history very similar to this one except that it was in younger patients. In children the disease was not fatal. These patients had been followed for a total of almost a year or more without much change in the character of the miliary lesion; they did, however, present an eosinophilia, — and there was no record of an eosinophilia in this patient, — but the type of lesion and the x-ray picture were not dissimilar to this, and the variation that occurred in this case could perhaps be confused with it. Usually the so-called eosinophilic pneumonias of the Loeffler type are more diffuse affairs, but they do occur in the miliary form. The onset in this case was somewhat bizarre, but the syndrome may be associated with some peculiar onset.

The condition may have been due to a fungus; coccidioidomycosis has been known to occur as a miliary lesion and to progress in all forms very similar to tuberculosis, but usually the diagnosis can be made and probably should have been made in this case by culture, had that been the diagnosis.

The bronchoscopic examination revealed remarkably little that was particularly helpful. There was a bilateral bronchitis, and the protocol did not state when the bronchoscopy was done.

Dr. Helen S. Pittman: I think the bronchoscopy was done before she became acutely ill.

Dr. Badger: The patient had a mild diffuse bronchitis; aside from that, nothing particular was found except a few cells that were of doubtful origin. I do not know what the record of your laboratory is in regard to doubtful cells; cells may be called doubtful in the presence of an inflammatory process from any cause, and they account for some of our false positives.

There are two other possibilities; one is adenomatosis of the lung. The bilateral symmetry is not necessarily characteristic of adenomatosis, and she lacks a rather important sign that is associated with that disease — that is, the abundant clear mucoid sputum that characteristically is secreted in fairly large quantities by the greatly enlarged alveolar cells, filled with mucoid globules. Although that is not a constant finding, if present in any significant amount it is suggestive of it. The bronchoscopic examination and cytologic study are not particularly helpful in that diagnosis. One has to judge rather by the progress of the disease unless a biopsy, lobectomy or pneumonectomy is performed. This could very well have been adenomatosis, but the diagnosis cannot be made on the studies of the secretions that were available.

On the whole, I am inclined to feel that the most logical and clinically the most likely diagnosis in this case is miliary carcinomatosis of the lung rather than granulomatosis, although I do not see how it is possible to tell. This woman's lesion was essentially localized in the lungs. There are no available diagnostic technics that we can apply to help make the diagnosis — no lymph nodes were available for biopsy, and there was no enlargement of the liver and spleen. The patient had a cough for three months, progressive dyspnea for three months, marked anorexia, progressive loss of weight, great weakness; those, together with a lesion of this sort at this woman's age that was not explainable on other bases, I think, may reasonably be considered carcinomatosis. The primary origin, as with other cases of carcinomatosis, may be a primary bronchogenic carcinoma with miliary metastases. That is my impression of this patient.

Dr. Benjamin Castleman: Dr. Badger, would you accept complete absence of enlarged hilar nodes with carcinomatosis?

Dr. Badger: It does occur — but not very often. It is difficult to diagnose that particular variety of case. A few years ago I saw a girl who had a miliary carcinomatosis with no evidence of enlargement of the nodes in the mediastinum until the very end. I would think that in the very last x-ray picture you might be suspicious that this patient was developing glandular enlargement, but I cannot put my finger on it.

Dr. Hanelin: The film was made with the patient in bed, so there is some distortion, and it is therefore difficult to be certain of any adenopathy.

Dr. Ernest M. Craige: Haven't almost all the cases of miliary carcinoma of the lungs originated in the pancreas in elderly persons?

DR. CASTLEMAN: In our material the stomach is probably the first source of metastatic cancer that has pulmonary lymphatic spread of metastases, with the pancreas second.

DR. BADGER: I, too, would put the stomach first. In this case I did not consider the stomach because it was called entirely normal by the radiologists. Carcinoma may have been present and not been seen radiologically.

A PHYSICIAN: How would you account for the bromsulfalein excretion and the alkaline phosphatase?

DR. BADGER: I cannot account for the elevated phosphatase; I am completely flabbergasted by it. Many patients can have a retention of 23 per cent bromsulfalein; they may have some intrinsic chronic liver disease. The patient may have had more than we know about, but the other tests were all negative; the bilirubin was essentially normal, the prothrombin time was normal and the cephalin flocculation I would call normal.

DR. JOSEPH C. AUB: I think that in a case like this the discusser should be told where the patient was born and what she did.

DR. CASTLEMAN: She was born in Massachusetts and was a housewife.

DR. PITTMAN: We did not know what was the matter with her. We went through all these conditions. We discovered that she never had any industrial exposures and that she had never been out of Massachusetts; being unable to arrive at any satisfactory decision from the information, we recommended lung biopsy. Before that could be carried out she spiked a high fever; in fact, it never was done, because she was in too poor condition.

DR. LEWIS KANE: I think I can safely say that this first x-ray film was a surprise and that when the patient was first seen the pulmonary symptoms were very few. I think almost everyone in the pulmonary group saw her at one time or another; about every diagnosis was made, including the correct one, but I do not think anyone was sure of the correctness of his own diagnosis.

CLINICAL DIAGNOSIS

Carcinoma of lung, left upper, with lymphatic spread.

DR. BADGER'S DIAGNOSIS

Miliary carcinomatosis of the lung.

ANATOMICAL DIAGNOSIS

Pulmonary adenomatosis, bilateral.
Cor pulmonale.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At the time of autopsy the lungs were very heavy, weighing almost 1800 gm., and both looked the same; they kept their contour and were firm and rubbery. When they were sectioned, there were throughout both lungs large confluent islands with a little intervening normal-appearing lung tissue. The islands were grayish white, homogeneous, not too granular — in fact, more smooth than granular; they reminded me in places of an organizing pneumonia. At the time of autopsy we did not know what the disease was; we thought first of metastatic carcinoma, although we could not rule out a granuloma of some sort. This slide shows a characteristic picture of what Dr. Badger mentioned — adenomatosis, whatever that

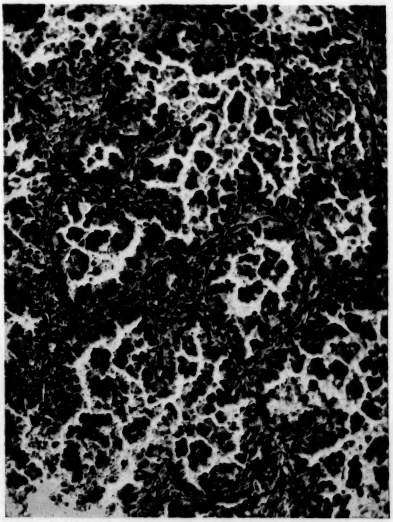

FIGURE 3.

is. In the alveolar spaces are found papillary processes lined with epithelial cells (Fig. 3). Some pathologists believe that these are the lining cells of the alveoli and therefore prefer to call this condition alveolar-cell carcinoma, assuming that the alveoli are lined with epithelial cells — an inference that has never yet been settled. This appearance is the same throughout all lobes of the lung. The next slide, a higher power, shows the benign character of these individual cells — no variation in size and shape and no mitoses. The diagnosis of adenomatosis is quite evident, but the one thing that is lacking, perhaps, is the mucoid secretion; that apparently has not been present in some of the other cases that have been reported. The lymph nodes were not involved and there was no evidence of any particularly

malignant-looking cells. There have been cases reported where the same picture was found in the regional lymph nodes and even beyond that; then one wonders whether that is the same condition or a true adenocarcinoma. I suppose there is a certain point at which further stimulation causes the condition to progress from benign to one that extends beyond the confines of the lung. Although the microscopical appearance is similar to jagziekte, a disease that occurs in sheep, there is no evidence that persons who have adenomatosis have ever been in contact with sheep.

We were unable to find any very striking change in the liver. There was some lymphocyte infiltration of the portal spaces and perhaps a little more congestion than one usually sees; I would not have expected it to produce any dysfunction of the liver.

DR. BADGER: What sort of "red herring" do you call the phosphatase now?

DR. CASTLEMAN: I cannot account for it.

DR. HARRIET HARDY: How long does this disease usually go on?

DR. BADGER: The duration of adenomatosis is about two to three years from the time the diagnosis is made. It is difficult to diagnose early because the patient has few or no symptoms. The longest recorded duration of adenomatosis, I believe, is eight years; I think it may have been much longer than that. A few of these patients have been operated on and lobectomies have been done. So far as I know it has never halted the development of the disease. As soon as the surgery is finished it progresses to the other lobe. It may originate in one lobe, rather than multicentrically, and progress from there. Progression over the years may be slow but rapid toward the end.

DR. CASTLEMAN: This patient's disease had existed for some time, as the right heart was about twice the normal thickness.

DR. KANE: An x-ray film of the left shoulder was taken about six months before the first chest film.

DR. HANELIN: I cannot be certain of pulmonary involvement from the portion of the lung included in the shoulder film.

DR. CASTLEMAN: If that is true, the disease extended over a period of about a year.

REFERENCES

1. Nemir, R. L., Heyman, A., Gorvoy, J. D., and Ervin, E. N. Pulmonary infiltration and blood eosinophilia in children (Loeffler's syndrome): review with report of eight cases. *J. Pediat.* **37**:819-843, 1950.
2. Weir, A. B. Jr. Pulmonary adenomatosis: clinical review and report of 3 cases. *Arch. Int. Med.* **85**:806-818, 1950.

CASE 38072

PRESENTATION OF CASE

A sixty-one-year-old man was admitted to the hospital because of gradual impairment of consciousness.

Six days before entry while driving home from work he felt faint, tired and sleepy so that he had to park his car at the curb. He rested two hours and then drove home. When he reached his home he was noted to have some slight slurring of his speech. There was no apparent difficulty in swallowing. On the following day he was fully conscious and was able to answer questions intelligently, but he had much more slurring of speech. He complained of a headache that was not relieved by aspirin. "Twitchings" of his eyes were observed at this time, and later that day his eyeballs rolled up spontaneously and repeatedly into a position of upward conjugate gaze. In the evening, he had a brief "shaking spell" with "shivering" but no loss of consciousness. Shortly thereafter his temperature was found to be 104°F. He was given one intramuscular injection of penicillin. His temperature returned to normal, but in addition to the slurring of speech he developed difficulty in swallowing and began to have constant side-to-side and up-and-down movements of the eyes. Two days prior to entry he was less responsive, had more difficulty in swallowing and became unable to speak, although he was able to follow commands. He was taken to another hospital, where the only abnormal physical findings were constant conjugate movements of the eyes, inability to speak and a blood pressure of 205 systolic, 90 diastolic. Lumbar puncture revealed 10 small lymphocytes per cu. mm. in the spinal fluid; a second puncture, made prior to admission, demonstrated 40 small lymphocytes per high-power field, 22 mg. of protein per 100 cc., 100 mg. of sugar per 100 cc. and a colloidal gold-sol curve of 0122100000. It was noticed that for a brief period the upper left half of his face was blanched, whereas the lower half was flushed.

Physical examination revealed a barely conscious, dehydrated, disorientated, unco-operative man, with Cheyne–Stokes respirations. The right pupil was 3 mm. in diameter, the left 4 mm.; both pupils reacted to light and dilated at distance. The optic disks were flat; the retinal arterioles were narrowed. There was no ptosis. There were almost constant movements of the eyes in all directions, most often conjugate but sometimes associated with skew deviation. During the few periods when the eyes were not moving in this manner, there was nystagmus to the left. The corneal reflexes were intact. There was a left-facial droop. He could not swallow, and there was a poor gag reflex. There was no paralysis of the vocal cords, which moved freely. He did not protrude the tongue on command. He was able to move all limbs with good strength. Tendon reflexes were moderately active and equal. Abdominal reflexes were present. There were bilateral extensor plantar reflexes. He reacted to pinprick on both sides of the face and forehead, on the abdomen and in all extremities. There was an aortic systolic murmur, but no other abnormalities were noted on general physical examination.

The temperature was 100.2°F., the pulse 100 and the blood pressure 162 systolic, 80 diastolic.

Examination of the blood showed a white-cell count of 12,150, with 89 per cent neutrophils and a hemoglobin of 16.5 gm. A urine examination was unremarkable.

The patient gradually sank deeper into coma. Continuous movements of the eyes persisted. On the second hospital day he did not move either arm but flexed and extended the legs several times. He was able to feel pinpricks in the limbs. Breathing became increasingly more difficult, with inspiratory stridor; the temperature rose to 103°F. on the second day and to 105°F. on the third day, and the patient died.

Differential Diagnosis

Dr. James B. Ayer*: In summarizing the points of special interest, the first is that nothing is said about past history. I do not know whether this man had had previous episodes or anything significant. Apparently he was well and able to drive his car. He developed on the first day slight slurring of speech in connection with the fatigue for which he had to stop his car. On the second day he showed real signs of a neurologic defect, with twitching of the eyes; apparently the eyes went upward and stayed there, — the so-called oculogyric crises, — but there were also fixed movements to the side, which I gather were conjugate movements and not individual eye movements or paroxysms of individual ocular muscles. By the third day the patient became less responsive but was still not in coma. He developed an aphonia, probably not aphasia. The blood pressure was elevated at that time. A lumbar puncture showed 10 lymphocytes with a normal protein and a very slight elevation of sugar. Unfortunately no serology was recorded. By the fifth day he still had the ocular symptoms, — forced movements of associated type, — but he later had skew deviation, one eye going up and the other going down — that is, dissociated ocular movements. The pupils were irregular but reacted to light and distance. It is important that there was no fixation of the pupils to light and no ptosis. The disks appeared normal but the vessels showed, I believe, arteriolar disease. The eye movements were probably the result of nystagmus. He had now developed the group of symptoms that fit the term "glossopharyngolabial paralysis" — a partial facial paralysis, inability to swallow and a poor gag reflex. Although there was no paralysis of the arms and legs there were bilateral Babinski reflexes. Between the sixth day and the ninth day, on which he died, there developed, — although there seemed to be nothing in the history about anything sudden, — rapid progression of the paralysis of the arms and paresis of the legs, apparently on both sides synchronously. He had hyperthermia that increased until his death. He was then in coma, and I think he had been so for three days, as far as I can make out. Notably absent were marked sensory disturbance and definite signs of nuclear involvement, although the hypoglossal nucleus may have been involved, as the patient could not move his tongue at all. No certain cerebellar signs were seen, although nystagmus may have been of cerebellar origin.

The clinical picture presented is characteristic of a rapidly progressive involvement of the brain stem. The earliest and most affected region concerns its upper portion, with profound eye signs but with disturbance of ocular control rather than nuclear destruction. That the disease rapidly descended into pons and medulla is suggested by progressive disturbance of speech, face and swallowing and finally by the respiratory death with hyperthermia after a course of only nine days.

Can I postulate a lesion above the brain stem? To produce such devastating signs a bilateral disturbance above the brain stem would have to be present. There was no evidence in the history of such. The patient was mentally intact at first; only later did he lapse into unconsciousness and coma. I see no evidence of cerebrovascular lesion causing "shock" or of tumor — certainly not bilaterally. I think I am entitled to say that the lesion is not solely above the brain stem. Some of the symptoms could be explained on the basis of disease above the brain stem. In particular, oculogyric crises are seen especially in postencephalitic Parkinsonism; the speech disturbance could have been due to pseudobulbar palsy at the beginning.

Can it have been a toxic or anoxic condition? Certainly phenobarbital can produce nystagmus, unsteadiness and death, but I am not aware that it leads to all the other signs. Carbon-monoxide and nitrous-oxide poisoning may kill, but they usually affect the cortex first, and the patient goes quickly into coma, with many other symptoms that were not present here — inco-ordinate movements of the limbs and so forth. I have never seen a case of botulism. According to the descriptions the eyes are the dominant feature; the pupils are said always to be dilated and fixed, and consciousness is retained until death. Perhaps someone who has seen botulism would say that this was such a case.

Can it have been a form of encephalitis beginning in the brain stem, or perhaps polioencephalitis? In the epidemic of encephalitis lethargica in 1918, 1919 and 1920, we saw a certain number of cases in which the maximal disturbance was in the brain stem, both clinically and pathologically. I would not exclude it because we do not happen to see it any more, although I have not seen such a case for years. There is one finding in the examination that makes me wonder. The cell count and the other spinal-fluid findings are very characteristic of an encephalitis. These cases are quite likely to have

*Member, Board of Consultation (formerly, chief of Neurology Service), Massachusetts General Hospital.

involvement of nuclei — for instance, a third-nerve or a sixth-nerve palsy. That was not the case here. These eye movements were associated and compulsive, at least in the beginning; then later there was skew deviation. The few cases of virus encephalitis that I have seen have been long-drawn-out cases with some brain-stem disturbance, but in many others in which the cortex was involved there was epilepsy, torsion spasm and choreoathetosis. There was nothing like that in this case. I would say that this case is not characteristic of the type of virus encephalitis that I have seen recently, and I would question encephalitis lethargica because we do not see it now. As for polioencephalitis there were no manifestations of "polio" involvement in the cord, nor does the clinical picture suggest primary involvement of nuclei, which is so characteristic of this disease.

That leaves me with the diagnosis I am quite certain is correct — a basilar-artery thrombosis. Basilar-artery thrombosis is a condition that is progressive over a period of just about this length of time, — somewhere between six and ten days, — and occurs without warning in a person who is receptive. For etiology, there is only the evidence of retinal arteriosclerosis and one blood pressure that was slightly elevated. The aortic murmur makes one think of a minute embolus perhaps moving up the basilar artery and lodging at the bifurcation of the posterior cerebral arteries, with thrombus starting there and growing downward. These symptoms, — I shall not enumerate them again, — fit in with the picture that is here presented. Among etiologic factors in thrombosis, I should mention aneurysm. I cannot find evidence of a basilar aneurysm in this case. There was no apoplectic attack and there was no blood in the fluid. However, a minute aneurysm might disturb the circulation. I believe an aneurysm is unlikely here.

One other possible etiology: Oppenheim,* in his textbook said, in the days before we had Wassermann reactions, that syphilis was the commonest cause of basilar thrombosis. In this case there were cells in the fluid, but no serology of the blood or the spinal fluid was mentioned. Could this have been syphilitic thrombosis?

*Oppenheim, H. *Die syphilitischen Erkrankungen des Gehirns.* Second edition. 200 pp. Vienna: A. Hölder, 1903.

I shall, then, make a definite diagnosis of basilar-artery thrombosis with these possible etiologies in mind, and, as a very poor second, some form of encephalitis.

DR. BENJAMIN CASTLEMAN: This patient was followed on the ward by Dr. Barrows, who arrived at the same diagnosis that Dr. Ayer made. Have you any comment, Dr. Barrows?

DR. LAWRENCE BARROWS: The man was placed in the respirator on the second hospital day and from that point on had to remain in the respirator in order to keep breathing. No one had seen these particular eye movements before; they are probably best likened to a pair of jiggling marbles in the sockets. They were continuous and initially were conjugate, but eventually there were some dysconjugate movements. The cells in the spinal fluid were reported from another hospital, where the counting was done without acetic acid and without stain, so we thought they might have been red cells at first. We made another count and found 40 lymphocytes. Those of us on the wards thought it was probably a basilar-artery occlusion due to syphilis.

DR. CASTLEMAN: I am a little skeptical of a basilar-artery thrombosis being due to syphilis. I have never been convinced that it has occurred in our material here. Do you know of any case, Dr. Kubik?

DR. CHARLES S. KUBIK: I do not recall any. I should like to emphasize a point brought out by Dr. Ayer; that is that virus encephalitis is so uncommon that one is always reluctant to make that diagnosis.

CLINICAL DIAGNOSIS

Basilar artery thrombosis.

DR. AYER'S DIAGNOSIS

Basilar artery thrombosis.
?Encephalitis.

ANATOMICAL DIAGNOSIS

Virus encephalitis.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Only the brain was examined. Dr. Richardson will tell you his findings.

DR. EDWARD P. RICHARDSON, JR.: The postmortem examination was performed outside the hospital and the already sectioned brain was sub-

mitted to us for study. Careful gross examination of this failed to reveal any thrombosis of any of the arteries, and no softenings or other lesions were grossly visible in the brain stem or elsewhere. Microscopical examination of the brain showed first of all a very marked perivascular infiltration of the small vessels, chiefly veins, with mononuclear cells, predominantly lymphocytes, a few large mononuclear cells and very few, if any, plasma cells. Similar small infiltrations were found in the subarachnoid space and were composed of the same sort of cells. In addition there were changes in the gray matter of the deep structures of the brain and of the brain stem, whereas the cerebral cortex was virtually intact. These changes consisted of a spotty disappearance of nerve cells and the presence here and there of obviously diseased, shrunken and distorted nerve cells. In such areas were large numbers of pleomorphic microglial cells. The changes were most marked in the thalamus and hypothalamus. These lesions were also present in the upper brain stem, in the pons and with diminishing frequency proceeding downward in the brain stem so that at the level of the medulla they were much less common than higher up. The cerebellum was likewise involved by this process and showed the same changes.

The constellation of these findings of an inflammatory disease with a mononuclear exudate and damage to the gray matter, as evidenced by disease of the nerve cells and the marked microglial reaction, is typical of infection with a neurotropic virus. We are unable to state which virus was the causative agent. It was pointed out as we reviewed the sections that the absence of cortical changes of any significant degree fairly well rules out such infections as St. Louis encephalitis, Japanese encephalitis and Eastern and Western equine encephalomyelitis. The degree of nerve-cell damage was not so severe as one would expect in infection with the poliomyelitis virus. The findings might fit in with encephalitis lethargica, but that is a disease that has not been seen for many years and I would be on rather shaky ground to make such a diagnosis without further evidence. It was not possible in this case to make any virus-isolation or serologic studies.

Dr. Ayer: The characteristic pathology of encephalitis lethargica shows involvement of both gray and white matter with the exudate around vessels.

Dr. Richardson: The exudate around the vessels is very prominent here.

Dr. Ayer: The ocular nerves were quite intact?

Dr. Richardson: No, these nuclei were not quite intact, but the nerve-cell damage was not as severe as we usually see in poliomyelitis.

Dr. Kubik: In acute poliomyelitis the nerve-cell damage is not nearly so pronounced in the brain stem as it is in the cord.

Dr. Ayer: I would be interested to know whether anybody else thought it was encephalitis in life.

Dr. Barrows: The diagnosis was not considered before death.

The New England Journal of Medicine

Formerly

The Boston Medical and Surgical Journal

Established 1828

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY
and
THE NEW HAMPSHIRE MEDICAL SOCIETY
OWNED BY THE MASSACHUSETTS MEDICAL SOCIETY AND PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. Richard E. Alt, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Clara D. Davies, EXECUTIVE EDITOR
Robert O'Leary, ASSISTANT EDITOR*

EDITORIAL BOARD
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. C. Stuart Welch, M.D.
Robert M. Green, M.D. Vernon P. Williams, M.D.
Dwight O'Hara, M.D. Benjamin Castleman, M.D.
Fletcher H. Colby, M.D. Hugh R. Leavell, M.D.
Robert L. Goodale, M.D. J. Englebert Dunphy, M.D.
Chester M. Jones, M.D. Robert W. Buck, M.D.
Harvey R. Morrison, M.D. Herrman L. Blumgart, M.D.
Deering G. Smith, M.D.†

*On leave of absence with the Armed Forces.
†Representing the New Hampshire Medical Society.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

THE JOURNAL does not hold itself responsible for statements made by any contributor.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

INSTITUTE OF ADMINISTRATIVE MEDICINE

IN JANUARY, 1952, Columbia University's Faculty of Medicine opened its Institute of Administrative Medicine, with Dr. E. Dwight Barnett, formerly the administrator of the Harper Hospital in Detroit, as its first director. Organized within the framework of the School of Public Health, the curriculum will combine a program of training graduate medical students in administration with extensive research "designed to determine the best methods for delivering maximum medical care to the American people at a reasonable cost."[1] In the dean's opinion the purpose of such training is to return the administration of health to the hands of specially trained members of the medical profession. The degree conferred after successful completion of the course will be in Administrative Medicine.

Successful medical administration, to judge by the performance of the country's ablest administrators, is based as firmly on a sound knowledge of medicine as on ability and training in administration. To administrate what? That is a question of primary importance, and the Columbia announcement defines five major areas of concern, to include hospital administration, prepayment medical care, public-health administration, industrial medical administration and medical-school administration.

The program, as outlined, is technical; the problems with which the Institute proposes to cope are basically biologic, even when framed in their professional, technical or economic setting — need for medical care; increasing age of the population; increased specialization of medical practice and need for teamwork; rapid growth of group insurance plans; the need for defining the role of the hospital in the future development of medical practice. Each of these considerations singled out for mention in the Columbia University announcement has a basis in human biology. Each is a matter of concern to sick patients and to practitioners, to the healthy population and to those whose efforts are directed toward the maintenance of health rather than the cure of disease. The complexities of the biologic problem demand that the future administrator be broadly grounded not only in clinical medicine and business administration but in mass problems that are the concern of epidemiology, biostatistics and public-health practice. For example, in the announcement describing the Institute reference is made to the need for "modern diagnostic laboratory facilities and personnel in many communities." The biologic questions "What do they need to diagnose?" and "What will the need be five years from now?" take precedence over the administrator's specific questions "How many laboratories do we need; where should they be placed; and by whom operated?" Likewise, in relation to growing insurance plans, as was pointed out by an able administrator, Dr. Dean A. Clark,[2] in the *Journal* of November 1, 1951, ". . . a more fundamental question than whether medical-care insurance should be voluntary or compulsory is what standards we should demand of any medical-care insurance."

A sound knowledge of both medicine and public health as well as methodology is needed by those who would try to find a way to deliver "maximum

medical care" to the American people at a reasonable cost. The problem of maximum medical care is primarily biologic, secondarily technical and thirdly economic. "First things first" should be a maxim if medical administration is really to become an important branch of medicine — if the new institute is to realize its worthy ambition of playing a "vital role . . . in giving the nation better medical care."

Columbia has set itself a difficult task and should be encouraged in this attempt to put instruction in administrative technics on a sound biologic and medical base. With such a base, instruction in administrative technics will provide another skill to be used for the better distribution of this care.

References

1. News Release, Public Information Office, Columbia University, New York, November 19, 1951.
2. Clark, D. A. "Two centuries of science — what of the next?" *New Eng. J. Med.* **245**:671-676, 1951.

LAND METHOD OF PROCESSING X-RAY FILMS

An epoch-making development in the processing of x-ray films has occurred. Most physicians have known of the Land camera, announced in 1947 as "a new one-step photographic process." Robbins and Land* have adapted this process to the x-ray film. No developing or processing laboratory is required. With this new process a positive print of a diseased site is available for inspection by the physician one minute after exposure to the x-rays. The Land X-Ray Pack is placed with an intensifying screen in a special cassette that resembles a standard cassette. This pack contains a negative sheet with a light-sensitive emulsion and a positive sheet with a special coating not sensitive to light on which the permanent positive radiograph is produced. To one edge of the sheet is attached a slender pod containing the processing agents in a fine jelly, which when subjected to pressure will be spread in a thin layer between the two sheets of specially prepared paper. The cassette may be loaded without a darkroom and handled thereafter as a standard cassette. When a cassette is to be used, a black envelope enclosing the negative sheet in the pack is pulled out of the cassette. The cassette is placed under the affected area and the film exposed. The cassette is then placed in a processing box in which motor-driven rolls spread the chemical reagents in a thin uniform film between the two special pieces of paper in the pack. In one minute the positive sheet containing the image is withdrawn. This photograph is instantly dry and ready for examination.

It is at once apparent that the speed of this new process will be extremely valuable in operating-room procedures, — the reduction of fractures and removal of foreign bodies, — and in accident cases, in critically ill patients and, particularly, in front-line military work. In fact, it is understood that the civilian use of the new process will be restricted until military requirements are satisfied. The new process has been tested at the Massachusetts General Hospital. The positive prints have been found to produce as much information as the films now in use, but more study may be needed, as this film is the reverse of the usual type. Somewhat more care in the use of the proper exposure factors is required, and at present a higher kilovoltage is necessary.

Certain limiting factors have been found. The prints are more easily scratched than are films, but a lacquer is being developed for coating them. The training of the roentgenologist has accustomed him to the negative transparent film, and considerable retraining will be required to enable him to perceive all the findings shown on the new positive print, which is viewed by reflected light. However, it is believed that transparent prints can be made available later. The prints at present are limited in size to 9 by 9 inches, but it is probable that larger and smaller prints can be made in the future.

The method is new, and it is inevitable that chemical and mechanical improvements will be devised so that this new ingenious process will render full service to roentgenology, to medicine in general and to the patient in particular.

*Robbins, L. L., and Land, E. H. Application of Land method of film processing in roentgenology. *J. A. M. A.* **147**:1217-1219, 1951.

"MEDICAL INTELLIGENCE"

The editors of the *Journal* have for some time felt the need of a little greater flexibility in its format to permit the more frequent publication of brief case reports, clinical notes, descriptions or new methods or instruments and other material of like or different nature. The intention is that this shall not replace any of the *Journal's* present content but shall constitute a new department to be used when suitable copy becomes available and space permits.

The selection of the title "Medical Intelligence" for this department does not represent, it is hoped, any substitution of a medical for the common variety of this indispensable attribute of the human mind but rather a recognition of its persistence over long periods, or even its reappearance in times of unusual stress. For the term "Intelligence," meaning, presumably, "information; news; advice" rather than "the ability to apprehend the interrelationships of presented facts in such a way as to guide action towards a desired goal," — for both of which definitions Mr. Webster is responsible, — designated a department in the newly-fledged *New England Journal of Medicine and Surgery* in 1812. Not only did this nomenclature persist until the establishment of the *Boston Medical and Surgical Journal* in 1828, but it reappeared in that estimable publication in 1830 as "Medical Intelligence," where it served its high purpose for over forty years, before going out of fashion.

Fashions, however, have always been cyclic in nature, and it is the hope of the editors that this revival of a descriptive name will meet with approval as well as elicit some suitable material for the occasional page or two that may be allotted to it.

SEVENTH POSTGRADUATE LECTURE COURSE

It is a pleasant editorial duty to call attention to another Postgraduate Lecture Course, — the seventh in the series, — that will be presented this season by the Massachusetts Medical Society in co-operation with the Massachusetts Department of Public Health.

For the third year since the flood tide of returning veterans receded, the lectures, which will be held on every Monday and Wednesday from March 3 to April 30, with the exception of March 17 and April 21, will be given in John Ware Hall at the Boston Medical Library. As before, the Monday exercises will occupy the hours from 7 to 9 p.m. and the Wednesday workouts those from 4 to 6 p.m.

The annual postgraduate lecture course, which has been planned and prepared with such painstaking care by the committee in charge, constitutes one of the most vital contributions that can be made to the health service of an area by the organizations that watch over it. Such service, strengthened by an expanding program of postgraduate education, has become a tradition within the Massachusetts Medical Society.

The "physicians of Massachusetts and surrounding states, medical officers, hospital residents, interns and medical students" who are invited to attend the lectures, regardless of their membership or non-membership in the Massachusetts Medical Society, cannot fail to be impressed with the sincerity of purpose that motivates such an undertaking.

MALLORY MEMORIAL FUND

The Trustees of the Massachusetts General Hospital have voted "to establish a special fund to be known as the Tracy Burr Mallory Memorial Fund to be used for some suitable memorial in the proposed new Pathology Building." Contributions to this fund may be sent to the Treasurer, Massachusetts General Hospital, 45 Milk Street, Boston.

Operation at the Massachusetts General Hospital. —

What particularly strikes the physician who in former years attended the operations at the hospital, is the strange contrast between the writhings and groans of the patient under the knife then, and the quiet stillness of the scene now. . . This change has been wrought by Ether, which has been sent, like a good angel, to bless poor suffering humanity.

Boston M. & S. J., *February 18, 1852*

MASSACHUSETTS MEDICAL SOCIETY

TREASURER'S OFFICE

This year the Committee on Finance has voted a refund of $4000 to the district societies from the surplus in the General Fund at the end of 1951.

Members are reminded that the percentage of this sum that is allocated to their own district is determined by the number of dues from that district paid by March 1, 1952. Members who have not paid their dues by this date are automatically removed from the mailing list of the *Journal* until such dues are paid.

Eliot Hubbard, Jr., *Treasurer*

TRACY BURR MALLORY

(1896–1951)

A life rich in experience, productivity and friendship was Tracy Mallory's. Distinguished pathologist and son of a distinguished pathologist, he graduated from Harvard College in 1918 and from Harvard Medical School, *magna cum laude*, at the top of his class, in 1921. His medical internship was at the Peter Bent Brigham Hospital. In 1925 he came to the Massachusetts General Hospital as chief of its Department of Pathology and Bacteriology, where he remained until his death. He reached the Harvard rank of professor of pathology at the Massachusetts General Hospital.

His scholarship was of a high order, and his interest was primarily in descriptive morbid anatomy. He sought in every case to achieve a clinicopathological correlation. This is well exemplified in his papers on carcinoma of the stomach *in situ*, his clinicopathological survey of lymphoma, his correlation of gastroscopic and pathological findings in gastritis and his work on infectious hepatitis, lower-nephron nephrosis and shock in the wounded.

He was a fine teacher. His well prepared lectures were warmly appreciated by students and faculty alike. He preferred, however, to talk to small groups, and even if only one student was present he would spend hours with him so long as the student showed interest.

His conduct of the clinicopathological conferences, founded by the Cabot brothers, was outstanding. His method was to broaden the base by putting a large number of clinicians on the spot to make diagnoses from the record.

His war service was distinguished, earning for him the Order of the Legion of Merit. As chief of the Pathology Section of the Fifteenth Medical General Laboratory, he served in North Africa and Italy. The laboratory was established in Naples for the duration, but Mallory went to the combat area in the winter of 1944 as officer in charge of a mobile unit to study shock. His greatest accomplishment, in the opinion of a fellow officer, lay in the high standards of medical observation and recording that he demanded and seemed to obtain almost as a matter of course. He became chief consultant in pathology for the entire Mediterranean Theatre; he was recognized everywhere, not only by his friends but by countless medical officers who knew only his name, as the great pathologist of the Mediterranean Campaign. A definite statement from him settled controversy to a degree that was true of no one else.

On the personal side, Tracy Mallory can be described as a man of great tenacity of purpose, forthrightness and intellectual honesty. His tastes were simple. He got his satisfactions in life quietly and unobtrusively.

Independence of thought and freedom of spirit were his in a way all too seldom seen in this regimented era. He always exercised his own judgment and formed his own opinions about men and their accomplishments. Detachment in appraisal in the face of emotional appeal is a rare quality, but Tracy Mallory possessed it. He had a great capacity for friendship. He also had great courage, both physical and moral. Evidence of the former can be found in his war service, of the latter in the meeting of his final illness.

Although the editors and the editorial board of the *Journal* knew Tracy as an outstanding pathologist and teacher, it was in his capacity as the editor of the Case Records of the Massachusetts General Hospital that they came to know him best and to admire his abilities and his personality. For in this capacity, although he rarely attended their meetings, he was one of them, in search of the best method of expression, striving for the greatest accuracy in the presentation of facts. His going is a great loss, not only to pathology, medicine and his friends but to the community.

POSTGRADUATE LECTURE COURSE

The seventh Postgraduate Lecture Course, which has been arranged by the Committee on Postgraduate Medical Education of the Massachusetts Medical Society, in co-operation with the Massachusetts Department of Public Health, will begin on March 3. The meetings will be held in John Ware Hall, Boston Medical Library, 8 Fenway, Boston. The lectures are designed for all physicians of Massachusetts and surrounding states (regardless of society membership), medical officers, hospital residents, interns, medical students and postgraduate students. Registration is free.

The detailed program of the course is as follows:

Monday, March 3. INFECTIOUS DISEASES AND ANTIBIOTICS. Chairmen: Drs. Louis Weinstein and Edward Kass.

7:00–7:25. **Treatment and Prophylaxis of Common Virus Infections.** Dr. Fred C. Robbins, associate physician-in-chief, Isolation Service, Children's Hospital; associate in pediatrics, Harvard Medical School.

7:25–7:50. **The Relation of Adrenal Hormones to Infectious Disease.** Dr. Edward Kass, instructor in medicine, Harvard Medical School; research fellow, Thorndike Memorial Laboratory; senior fellow in virus diseases, National Research Council.

7:50–8:15. **The Selection of Antibiotics.** Dr. Chester S. Keefer, physician-in-chief, Massachusetts Memorial Hospitals; director, Evans Memorial Hospital; Wade Professor of Medicine, Boston University School of Medicine.

8:15–8:40. **Untoward Reactions to Chemotherapy.** Dr. Louis Weinstein, associate professor of medicine, Boston University School of Medicine; chief, Infectious Disease Service (Haynes Memorial), Massachusetts Memorial Hospitals; lecturer in infectious diseases, Harvard Medical School.

8:40–9:00. **Newer Problems in the Use of Antibiotics.** Dr. Maxwell Finland, associate professor in medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; associate director, Thorndike Memorial Laboratory.

Wednesday, March 5. CARDIOLOGY. Chairmen: Drs. Gordon S. Myers and Herrman L. Blumgart.

4:00–4:30. **Curable Forms of Heart Disease.** Dr. Laurence B. Ellis, associate physician (Thorndike Memorial Hospital), Boston City Hospital; assistant visiting physician, Boston City Hospital; chief of Cardiac Clinic, Boston City Hospital; consultant in medicine, Cushing Veterans Administration Hospital, U. S. Public Health Hospital, Brighton, and Chelsea Naval Hospital; assistant clinical professor of medicine, Harvard Medical School.

4:30–5:00. **False Diagnosis of Heart Disease.** Dr. A. Stone Freedberg, assistant professor of medicine, Harvard Medical School; associate director of medical research, Beth Israel Hospital.

5:00–5:30. **Indications and Contraindications for Anticoagulant Therapy.** Dr. Lewis Dexter, assistant professor of medicine, Harvard Medical School; senior associate in medicine, Peter Bent Brigham Hospital.

5:30–6:00. **The Use of Veratrum Alkaloids in Arterial Hypertension.** Dr. Edward Meilman, instructor in medicine, Harvard Medical School; associate in medical research, Beth Israel Hospital.

Monday, March 10. CARDIOLOGY: PREVENTION OF HEART DISEASE. Chairmen: Drs. Gordon S. Myers and Herrman L. Blumgart.

7:00–7:30. **Prevention of Recurrent Rheumatic Fever.** Dr. Ernest Craige, assistant in medicine, Harvard Medical School; assistant in medicine, Massachusetts General Hospital; assistant visiting physician, House of Good Samaritan.

7:30–8:00. **Prevention of Bacterial Endocarditis.** Dr. Maxwell Finland, associate professor of medicine, Harvard Medical School; chief, Fourth Medical Service, Boston City Hospital; associate director, Thorndike Memorial Laboratory.

8:00–8:30. **Present Status of Prevention of Atherosclerosis.** Dr. Howard B. Sprague, chief of staff, House of Good Samaritan; associate physician, Massachusetts General Hospital; clinical associate in medicine, Harvard Medical School.

8:30–9.00. **Prevention of Recurrent Myocardial Infarction.** Dr. Paul M. Zoll, associate in medicine, Harvard Medical School; associate visiting physician, Beth Israel Hospital.

Wednesday, March 12. OBSTETRICS. Chairmen: Drs. Duncan E. Reid and Arthur T. Hertig.

4:00–4:25. **Carcinoma of the Ovary in Pregnancy.** Dr. H. Jane C. MacMillan, assistant pathologist, Peter Bent Brigham Hospital; instructor in pathology, Harvard Medical School.

4:25–4:50. **Carcinoma in Situ of the Cervix in Pregnancy.** Dr. Arthur T. Hertig, acting head of pathology, Harvard Medical School; pathologist, Boston Lying-in Hospital and Free Hospital for Women; consultant at Carnegie Institution, Washington, D. C., and Chelsea Naval Hospital.

4:50–5:15. **Problems of Current Interest in Neonatal Pediatrics.** Dr. Clement A. Smith, associate professor of pediatrics, Harvard Medical School; chairman, Department of Pediatrics, Infants' Hospital, Children's Medical Center.

5:15–5:40. **The Differential Diagnosis of First-Trimester Uterine Bleeding.** Dr. Crawford Hinman, staff, Boston Lying-in Hospital, Free Hospital for Women and Faulkner Hospital; associate professor of obstetrics, Harvard Medical School.

5:40–6:00. **Clinical Implication of Uteroplacental Aging.** Dr. Seymour Romney, assistant in obstetrics, Boston Lying-in Hospital and Free Hospital for Women.

Wednesday, March 19. ENDOCRINOLOGY. Chairmen: Drs. Lewis M. Hurxthal and Anna P. Forbes.

4:00–4:40. **Film on ACTH.** Courtesy of Armour Company.

4:40–5:05. **The Use of ACTH and Cortisone in Rheumatic and Allied Diseases.** Dr. W. S. Clark, instructor in medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

5:05–5:30. **The Use of ACTH and Cortisone in Allergic and Allied Diseases.** Dr. Robert P. McCombs, professor of graduate medicine, Tufts College Medical School; physician, Pratt Diagnostic Clinic and New England Medical Center.

5:30–5:50. **The Use of ACTH and Cortisone in Eye Diseases.** Dr. Edwin P. Dunphy, Henry W. Williams Professor of Ophthalmology, Harvard Medical School; chief of ophthalmology, Massachusetts Eye and Ear Infirmary.

5.50–6:00. **Questions and answers.**

Monday, March 24. ENDOCRINOLOGY. Chairmen: Drs. Lewis M. Hurxthal and Anna P. Forbes.

7:00–7:30. **Endocrine Disorders of Infancy.** Dr. Nathan B. Talbot, associate professor of pediatrics, Harvard Medical School; physician, Massachusetts General Hospital.

7:35–8:05. **Metabolic Bone Disease.** Dr. Anna P. Forbes, assistant in medicine, Harvard Medical School and Massachusetts General Hospital.

8:10–8:40. **Menopause.** Dr. Somers E. Sturgis, assistant clinical professor of gynecology, Harvard Medical School; senior associate in surgery, Peter Bent Brigham Hospital; consultant in gynecology, Children's Hospital.

8:40–9:00. **Questions and answers.**

Wednesday, March 26. *4:00–6:00* p.m. GASTROINTESTINAL DISEASES. Chairmen: Drs. Alexander J. A. Campbell and S. Allen Wilkinson.

SYMPOSIUM

The Medical and Surgical Treatment of Peptic Ulcer. Chairman: Dr. Alexander J. A. Campbell.

Dr. C. Stuart Welch, professor of surgery, Tufts College Medical school; surgeon-in-chief, New England Center Hospital.

Dr. Benjamin M. Banks, clinical associate in medicine, Harvard Medical School; associate physician and chief, Gastrointestinal Clinic, Beth Israel Hospital.

Dr. Merrill C. Sosman, professor of roentgenology, Harvard Medical School; roentgenologist-in-chief, Peter Bent Brigham Hospital.

Dr. S. Allen Wilkinson, Department of Gastroenterology, Lahey Clinic; physician, New England Baptist and New England Deaconess hospitals.

Dr. Stanley L. Robbins, assistant professor of pathology, Tufts College Medical School; assistant pathologist, Boston City Hospital.

Dr. Alexander J. A. Campbell, associate clinical professor of surgery, Tufts College Medical School; visiting surgeon, Boston City Hospital.

Monday, March 31. GASTROINTESTINAL DISEASES. Chairmen: Drs. Alexander J. A. Campbell and S. Allen Wilkinson.

The Medical and Surgical Management of Jaundice. Chairman: Dr. S. Allen Wilkinson.

7:00–7:25. **The Differential Diagnosis of Jaundice on the Basis of History.** Dr. Franz J. Ingelfinger, associate professor of medicine, Boston University School of Medicine; visiting physician, Massachusetts Memorial Hospitals.

7:25–7:50. **The Use of Limitations of Liver-Function Tests.** Dr. Perry J. Culver, associate in medicine, Harvard Medical School; assistant physician, Massachusetts General Hospital.

7:50–8:15. **The Pathology of the Liver in Biliary Xanthomatosis.** Dr. H. Edward MacMahon, professor of pathology, Tufts College Medical School; pathologist, New England Medical Center.

8:15–8:40. **Cholorrhea Following Biliary-Tract Surgery.** Dr. David D. Berlin, clinical professor of surgery, Tufts College Medical School; visiting surgeon, Beth Israel and Boston City hospitals.

8:40–9:00. **Ampullary and Periampullary Tumors.** Dr. Kenneth W. Warren, Department of General Surgery, Lahey Clinic; surgeon, New England Baptist and New England Deaconess hospitals.

Question period.

Wednesday, April 2. KIDNEY — MEDICAL AND SURGICAL ASPECTS. Chairmen: Drs. Walter S. Kerr, Jr., and John P. Merrill.

4:00–4:20. **The Treatment of Renal Insufficiency.** Dr. John P. Merrill, instructor in medicine, Harvard Medical School; associate in medicine, Peter Bent Brigham Hospital; established investigator, American Heart Association.

4:30–4:50. **Use and Abuse of Diuretics.** Dr. William B. Schwartz, visiting physician, New England Center Hospital; associate professor of medicine, Tufts College Medical School.

5:00–5:20. **Renal Tuberculosis.** Dr. Fletcher H. Colby, chief, Urological Service, Massachusetts General Hospital.

5:30–5:50. **Antibiotics and Kidney Infections.** Dr. Walter S. Kerr, Jr., assistant in urology, Massachusetts General Hospital.

Monday, April 7. DISORDERS OF ELECTROLYTE METABOLISM. Chairmen: Drs. Arnold S. Relman and William B. Schwartz.

7:00–7:20. **Effects of Electrolyte Disorders on the Electrocardiogram.** Dr. John P. Merrill, instructor in medicine, Harvard Medical School; associate in medicine, Peter Bent Brigham Hospital; established investigator, American Heart Association.

7:30–7:50. **Electrolyte Metabolism in Gastrointestinal Disorders.** Dr. William Wallace, physician, Children's Medical Center; assistant professor of pediatrics, Harvard Medical School.

8:00–9:00. **Round-Table Discussion of Postoperative Electrolyte Disorders.**

Dr. John Raker, instructor in surgery, Massachusetts General Hospital.

Dr. Alexander Leaf, clinical and research associate in medicine, Massachusetts General Hospital; research fellow in medicine, Harvard Medical School.

Dr. Arnold S. Relman, associate member, Evans Memorial Hospital; assistant professor of medicine, Boston University School of Medicine.

Dr. William B. Schwartz, visiting physician, New England Center Hospital; assistant professor of medicine, Tufts College Medical School.

Wednesday, April 9. *4:00–6:00* p.m. PANEL DISCUSSION ON FRACTURES ABOUT THE ELBOW JOINT IN CHILDREN. Chairmen: Drs. Russell F. Sullivan and Carter R. Rowe.

Dr. Russell F. Sullivan, professor of orthopedic surgery, Tufts College Medical School; surgeon-in-chief, Orthopedic Service, Boston City Hospital; surgeon-in-chief, Orthopedic Service, Malden Hospital.

Dr. Carter R. Rowe, assistant in orthopedic surgery, Harvard Medical School and Massachusetts General Hospital.

Dr. George W. Van Gorder, Board of Consultation, Orthopedic Service, Massachusetts General Hospital; chief, Orthopedic Service, Newton-Wellesley Hospital.

Dr. Alexander P. Aitken, clinical professor of orthopedic surgery, Tufts College Medical School; senior visiting orthopedic surgeon, Boston City Hospital.

Dr. David F. Grice, orthopedic surgeon, Children's Hospital; instructor in orthopedic surgery, Harvard Medical School.

Dr. E. Everett O'Neil, clinical professor of surgery, Boston University School of Medicine; surgeon-in-chief, Boston University Teaching Service, Boston City Hospital.

Dr. Paul I. O'Brien, assistant in orthopedic surgery, Tufts College Medical School; teaching fellow, Orthopedic Service, Boston City Hospital.

Monday, April 14. *7:00–9:00* p.m. PANEL DISCUSSION ON PERIPHERAL VASCULAR DISEASES. Chairmen: Drs. Edward A. Edwards and Joseph R. Stanton.

Dr. Robert Linton, chief of Peripheral Vascular Clinic, Massachusetts General Hospital; assistant clinical professor of surgery, Harvard Medical School; visiting surgeon, Massachusetts General Hospital.

Dr. Theodore C. Pratt, surgeon, New England Deaconess Hospital; associate surgeon, Palmer Memorial Hospital; consultant, U. S. Naval Hospital, Chelsea.

Dr. Robert Wilkins, associate professor of medicine, Boston University School of Medicine; visiting physician, Massachusetts Memorial Hospitals; member, Robert Dawson Evans Memorial Hospital.

Dr. Edward A. Edwards, associate in surgery, Peter Bent Brigham Hospital; assistant clinical professor of anatomy, Harvard Medical School.

Dr. Joseph R. Stanton, instructor in medicine, Boston University School of Medicine; research fellow, Robert Dawson Evans Memorial Hospital; assistant in medicine, St. Elizabeth's Hospital.

Wednesday, April 16. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30. **Practical Methods for the Evaluation of Pulmonary Function.** Dr. Edward A. Gaensler, assistant visiting surgeon, Thoracic Surgery Service, Boston City Hospital; assistant in medicine, Harvard Medical School; assistant in surgery, Boston University School of Medicine.

4:30–5:00. **The Significance of Hemoptysis.** Dr. Carlton R. Souders, Department of Internal Medicine, Lahey Clinic; physician, New England Deaconess and New England Baptist hospitals.

5:00–5:30. **Hidden Bronchiectasis in the Asthmatic Patient.** Dr. James H. Walker, staff, New England Deaconess and Cambridge City hospitals; assistant instructor in surgery, Tufts College Medical School.

5:30–6:00. **The Value of the Boston Chest X-Ray Survey.** Dr. John H. Cauley, medical staff, Boston City Hospital; visiting staff, St. Margaret's Hospital, Dorchester; assistant professor, Harvard School of Public Health; Health Commissioner, City of Boston.

Wednesday, April 23. CHEST DISEASES. Chairmen: Drs. Carlton R. Souders and Richard H. Overholt.

4:00–4:30. **The Management of Esophageal Lesions.** Dr. Herbert D. Adams, general and thoracic surgeon, Lahey Clinic, New England Deaconess and New England Baptist hospitals; thoracic consultant, Chelsea Naval Hospital.

4:30–5:00. **Modern Aspects of the Surgical Treatment of Tuberculosis.** Dr. John W. Strieder, surgeon-in-chief of thoracic surgery, Boston City Hospital, Boston City Hospital Sanatorium at Mattapan and Newton–Wellesley Hospital; clinical professor of thoracic surgery, Boston University School of Medicine.

5:00–5:30. **An Evaluation of X-Ray Therapy for Intrathoracic Lesions.** Dr. Laurence L. Robbins, radiologist-in-chief, Massachusetts General Hospital; assistant professor of radiology, Harvard Medical School.

5:30–6:00. **The Cancer Potential of Silent Pulmonary Shadows.** Dr. Richard H. Overholt, thoracic surgeon, New England Deaconess and New England Center hospitals; clinical professor of surgery, Tufts College Medical School.

Monday, April 28. PEDIATRICS. Chairmen: Drs. Nathan B. Talbot and James M. Baty.

7:00–7:25. **Recognition of Correctible Congenital Heart Disease.** Dr. Gordon S. Myers, assistant physician, Massachusetts General Hospital; assistant in medicine, Harvard Medical School.

7:25–7:50. **Recognition of Correctible Congenital Malformations of the Gastrointestinal Tract.** Dr. Orvar Swenson, surgeon-in-chief, Boston Floating Hospital; associate professor of surgery, Tufts College Medical School.

8:00–8:25. **Problems of Adolescence in Girls.** Dr. Janet McArthur, assistant physician, Massachusetts General Hospital; instructor in gynecology, Harvard Medical School.

8:25–8:50. **Problems of Adolescence in Boys.** Dr. J. Roswell Gallagher, physician in charge of Adolescent Services, Children's Medical Center.

8:50–9:00. **Discussion.**

Wednesday, April 30. THE DIAGNOSTIC AND THERAPEUTIC APPLICATIONS OF RADIOACTIVE ISOTOPES. Chairmen: Drs. Shields Warren and Joseph F. Ross.

4:00–4:10. **Introduction**: Dr. Shields Warren, professor of pathology, Harvard Medical School; pathologist, New England Deaconess Hospital; director, Division of Biology and Medicine, United States Atomic Energy Commission.

4:10–4:30. **The Nature of Radioactive Isotopes and the Biologic Effects of Their Radiations.** Dr. Sanborn C. Brown, associate professor of physics, Massachusetts Institute of Technology.

4:30–4:50. **Therapeutic Applications of Radiogold, Radiocobalt and Other Mechanically Positioned Isotopes in the Treatment of Cancer.** Dr. Marshall Brucer, chairman, Medical Division, Oak Ridge Institute of Nuclear Studies, Oak Ridge, Tennessee.

4:50–5:10. **The Treatment of Leukemia and Polycythemia Vera with Radioactive Phosphorus.** Dr. Joseph Ross, associate professor of medicine, Boston University School of Medicine; physician, Massachusetts Memorial Hospitals; director, Radioisotope Unit, Cushing Veterans Administration Hospital.

5:10–5:30. **The Diagnosis and Treatment of Thyroid Diseases with Radioactive Iodine.** Dr. Belton A. Burrows, assistant professor of medicine, Boston University School of Medicine; physician, Radioisotope Unit, Cushing Veterans Administration Hospital; associate visiting physician, Massachusetts Memorial Hospitals.

5:30–5:50. **Localization of Tumors with Radioactive Isotopes.** Dr. William H. Sweet, assistant professor of surgery, Harvard Medical School; visiting neurosurgeon, Massachusetts General Hospital.

5:50–6:00. **Discussion.**

BOSTON MEDICAL LIBRARY

NOBEL PRIZES

In the *Münchener Medizinische Wochenschrift* for 1951 (**93**:1149, 1223, 1272) Dr. Joseph Schumacher lists in chronologic order the recipients of the Nobel Prize in physiology and medicine, from the first, Emil von Behring (1901), to the 1950 joint winners, Tadeus Reichstein of Basel and E. C. Kendall and P. S. Hench of the Mayo Clinic. This valuable compilation has been reprinted in a six-page folio pamphlet. In this connection, the book recently published by the Nobel Foundation, — *Nobel, the Man and His Prizes* (Norman, Oklahoma, 1951), — is also of interest.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

ALCOHOL-ANTABUSE REACTION

In 1948, Antabuse, or tetraethylthiuram disulfide, was made available to certain selected physicians for the purpose of carrying on controlled clinical studies on the treatment of alcoholism or alcohol addiction. However, since October, 1951, Antabuse has been released for general medical practice and to all physicians. Since a severe reaction may occur on the ingestion of alcohol in those persons undergoing treatment with this drug, it behooves all physicians to become acquainted with the symptoms of the alcohol-Antabuse reaction.

Antabuse taken alone produces few or no symptoms. On the other hand, when alcohol in any form, as in spirituous liquors, beer, wine, elixirs, cough mixtures and so forth, is introduced, a characteristic response occurs. The intensity and duration of symptoms depend on the dosage of the drug, the amount of alcohol ingested and the specific sensitivity of the individual. After administration of Antabuse, a period of at least three hours is necessary before ingestion of alcohol will produce any symptoms, and twelve to twenty-four hours are

required for a definite effect. Mild reactions may occur in a sensitive person when the blood-alcohol concentration is increased to as little as 5 to 10 mg. per 100 cc. At 50 mg. per 100 cc. symptoms are fully developed, and the subject becomes unconscious when the blood-alcohol level reaches 125 to 150 mg. per 100 cc. The duration of the reaction varies from thirty to sixty minutes to several hours in the more severe cases, or as long as there is any alcohol in the blood. Even if Antabuse therapy is discontinued, the patient remains conditioned against alcohol for seven to ten days, because of the relatively slow elimination of the drug from the body.

Although the exact mechanism of action is not yet known, a probable explanation is the increased accumulation of acetaldehyde in the blood and tissues when administration of Antabuse is followed by ingestion of alcohol. It may be that Antabuse interferes with the normal oxidation of alcohol in the body beyond the acetaldehyde stage.

When a moderate amount of alcohol is ingested (15 to 30 cc. or ½ to 1 oz. of 100-proof whiskey), the following symptoms usually occur: flushing of the face in five to fifteen minutes, with gradual increase in intensity to a purplish red; vasodilatation of the scleras, with slight edema of the lower eyelids; extension of flushing to the upper thorax and arms; rapid pulse or tachycardia; some dyspnea with hyperventilation; and unaltered or slightly depressed blood pressure.

When larger amounts of alcohol are ingested (80 to 100 cc. or 2 to 3 oz. or more of 100-proof whiskey) all these symptoms are intensified; pulmonary ventilation is markedly increased, the pulse rate may reach 120 to 140 and there may be other manifestations of cardiac stress. Nausea and vomiting may occur, and the intense flushing may give way to pallor. Both systolic and diastolic blood pressure drop considerably — sometimes alarmingly, in a shock-like manner. The consciousness may be clouded, and coma may even ensue.

No specific antidote is yet available, but various measures have been suggested to control and lessen the severity of the reaction, such as oxygen inhalation, cardiovascular stimulants (coramine or ephedrine) and intravenous administration of fluids or massive doses of Vitamin C.

The alcohol-Antabuse reaction may be confused with many other conditions, such as head injury, epileptic seizure, diabetic coma, cerebrovascular accident and the like. The odor of alcohol on the breath may be misleading; hence a diagnosis of acute intoxication may be made, with possible serious and even fatal consequences. The importance of differentiating acute intoxication, alcohol-Antabuse reaction and other conditions cannot be overemphasized.

The patient's clothing should be searched for Antabuse tablets and Antabuse identification cards or "dog tags." A history of Antabuse therapy should be, if possible, elicited from the patient or from friends or relatives. Moreover, determinations of blood alcohol and acetaldehyde levels should be carried out whenever possible, particularly in questionable cases.

JOHN C. AYRES, M.D., *Director*
Division of Alcoholism

CORRESPONDENCE

MORE ON ALCOHOL INHALATION

To the Editor: I have noted the letter from Dr. Luisada, published in the *Journal* of January 3, referring to our article on "Inhalation of Ethyl Alcohol for Pulmonary Edema," published in the November 29 issue of the *Journal*. The point of the letter appears to be that Dr. Luisada had used the method clinically prior to the publication of our report.

Of course, we have no way of knowing in how many places alcohol inhalation is being tried out. Discussions of priority are seldom rewarding, and we are glad to reiterate our indebtedness to Dr. Luisada's experimental work, but we do wish to point out that our work with alcohol inhalation was begun on the basis of the published experimental data, months before the earliest report of clinical application. Our report was written and submitted for publication before the fall meeting at the New York Academy of Medicine, and both the patients reported, as well as a number of others, had been treated before June, 1951, the date of the very first verbal report claimed by Dr. Luisada. Moreover, we addressed ourselves not merely to the matter of administering alcohol inhalation but to the problem of combining that drug with oxygen under pressure.

Our experience with this method of treating pulmonary edema continues to be encouraging, and we hope in the future to incorporate this growing experience in a more comprehensive report.

ABRAHAM GOOTNICK, M.D.
Brooklyn, New York

UNEASY COMPROMISE

To the Editor: With numerous articles appearing in the lay press extolling the British system of medicine, I thought the following extract from a letter to me from a good friend in New Zealand, high in the councils of the British Medical Association there, might be of interest to your readers:

> We maintain an uneasy compromise with the Government on the present health scheme which preserves the freedom of the profession at considerable cost to the tax payer. One of your people said socialized medicine was like death — you just couldn't have a little bit of either. I fear we are at least dangerously ill. *What an awful mess they have made of it in England. There are thousands of English doctors trying to get to this small dominion and the number coming in is one of our worst problems.* (Italics mine.)

FRANCIS T. HUNTER, M.D.
Boston

NONCLINICAL NOTE

DR. FLEMING ACCEPTS NEW POST

Dr. William L. Fleming, since 1946 professor of preventive medicine at Boston University School of Medicine and chief of the Genitoinfectious Disease Clinic at the Massachusetts Memorial Hospitals, has resigned these posts to return to the University of North Carolina to become professor of preventive medicine at that institution.

Dr. Fleming has retired also from the presidency of the Massachusetts Society for Social Hygiene, Inc. He has been succeeded in this position by Dr. Chester N. Frazier, Edward Wigglesworth Professor of Dermatology at Harvard Medical School and chief of the Dermatological Service at Massachusetts General Hospital.

MISCELLANY

WORLD HEALTH ASSEMBLY

The Executive Board of the World Health Organization met in Geneva in January to plan for the Fifth Health Assembly, to be held in May, also in Geneva.

Reports were reviewed from 12 expert committees on nursing, maternity care, alcoholism, sanitation, statistics and other important health topics. Budget proposals for the 1953 program, to be submitted to the Assembly, were also prepared, in line with recommendations of the Standing Committee on Administration and Finance.

BOOK REVIEWS

Scoliosis: Pathology, etiology, and treatment. By Samuel Kleinberg, M.D. 8°, cloth, 286 pp., with 163 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $7.50.

It is not easy to write an acceptable book on scoliosis, a subject so complicated by misconceptions and controversy. In this book the known facts are presented without bias and as satisfactorily as possible. At no time does the author lose his way in the maze of poorly understood mechanisms or unproved therapeutic procedures.

The book begins with a discussion of the anatomy, pathology and etiology of scoliosis. Efficient methods of recording the progress of scoliosis are recorded. Prevention, almost completely neglected by both parents and physicians, is ably presented. Treatment, both conservative and operative, is presented in detail, with many illustrations. The author is optimistic, as any one must be who treats many cases of scoliosis. He states that all satisfactory end results in scoliosis are probably evidence of adequate compensation and the establishment of stability through muscular training. Ten to 20 per cent of all patients with scoliosis require operative treatment. Operation should not be considered when the curve is mild or stationary or in the very young or in the asthenic. Operative treatment is indicated in paralytic scoliosis, progressive deformity, failure of conservative treatment, severe familial scoliosis, cervicodorsal kyphoscolioses and persistent pain with dorsal curvature in adults. Various operative procedures are discussed. A complete bibliography is included. The illustrations are excellent. The book is written in a clear, pleasant conversational style. This is a sound book and should be helpful to all physicians who treat scoliosis.

JOHN G. KUHNS, M.D.

Reality and Dream: Psychotherapy of a Plains Indian. By George Devereux, Ph.D. With prefaces by Karl A. Menninger, M.D., and Robert H. Lowie, Ph.D., and psychological tests edited and interpreted by Robert R. Holt, Ph.D. 8°, cloth, 438 pp., with 13 illustrations and 12 plates. New York: International Universities Press, 1951. $7.50.

This book presents a complete verbatim transcript of the psychoanalytic "expressive-supportive" therapy of a thirty-three-year-old American Indian patient who presented a variety of neurotic symptoms against the background of a basically schizoid personality. Because of the patient's ethnic background a substantial portion of the book is devoted to the author's hypotheses about the relation between Plains Indian culture and Indian personality development. In addition, the full protocols of all psychologic tests administered both before and after the therapy are included; these were edited and interpreted by Dr. Robert R. Holt. The approach is thus interdisciplinary, since it draws on anthropology, psychoanalysis and projective psychology for its conceptual frames of reference.

Within each discipline, however, the author has taken certain liberties. For example, as an anthropologist he offers the novel suggestion that any Indian's individual personality is more deeply molded by a generic areal pattern (for example, Plains Indian) than by the differential of his specific tribe (such as Sioux). A fervent lay analyst who describes his authoritarian dream analysis as "transcultural therapy," he nevertheless claims to have achieved a satisfactory approximation to his therapeutic objective in only thirty hours.

As regards the psychologist's contribution, the author is especially adroit. Despite findings pointing to the unstable equilibrium achieved by the patient after therapy and indications that any future changes would be toward a less healthy state, the author still proclaims a successful outcome for his treatment. In other words, the patient appears to have learned to abandon some of his neurotic defenses and to accept himself as a person who does not seek to establish warm emotional contact with others. During the year following his discharge from the hospital the patient was heard from on two occasions. The first was a peculiarly worded telegram (not reproduced) in which he repudiated one of the principal conclusions he had reached in his therapeutic interviews. Devereux thinks the patient was drunk when he wrote it. The second occasion occurred a year later, when the patient wrote to the author requesting a loan and adding: "I have been well from all my worries since I left you." In order to claim success the author must assert that this is a typical picture of the average, symptom-free Plains Indian and that a proper therapeutic objective is always to "restore the patient to himself." Whether or not this proposition is true cannot be judged by a reader unfamiliar with healthy Plains Indians, since norms for this population are not available.

Regardless of the validity of Devereux's evaluation of his own therapeutic skill, however, this book can be warmly recommended for its multidimensional study of the complex and fascinating interrelation of culture and personality within a single person.

CHARLES P. FONDA, PH.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

John Hunter. By S. Roodhouse Gloyne, M.D. (Leeds), consulting pathologist, London Chest Hospital and King Edward VII Sanatorium, Midhurst. 8°, cloth. 104 pp., with 16 illustrations and frontispiece. Baltimore: The Williams and Wilkins Company, 1950. $3.50.

This new monograph on John Hunter considers him in his contemporary setting, with its varying influences. Although Hunter did not make any fundamental medical discoveries, he influenced British medicine of the eighteenth century greatly by encouraging medical research in all its branches; he also established the Hunterian Museum of the Royal College of Surgeons in London. The text is well written and the publishing excellent. The book should be in all collections on the history of medicine.

The Early Diagnosis of the Acute Abdomen. By Zachary Cope, M.D., M.S. Lond., F.R.C.S. Eng., consulting surgeon to St. Mary's Hospital, Paddington, and to the Bolingbroke Hospital, Wandsworth Common. Tenth edition. 8°, cloth, 270 pp., with 39 illustrations. New York: Oxford University Press, 1951. $3.50. (Oxford Medical Publications.)

The monograph of Dr. Cope was first printed in 1921; eighteen printings in ten editions are proof of its sound value. Only a few minor alterations have been made in this edition. The printing is well done, with a good type, and there is a good index. One of the two last editions should be in all medical libraries and available to all physicians interested in the subject.

Let's Cook it Right: Good health comes from good cooking. By Adelle Davis, M.S. 8°, cloth, 626 pp. New York: Harcourt, Brace and Company, 1947. $3.00.

This new cookbook combines the principles of nutrition with the preparation of the various classes of foods. Miss Davis presents 350 basic recipes, with over 3000 variations for every kind of food. Especial attention is paid to meats, because of their cost, and vegetables, because they are usually robbed of their important nutrients during ordinary cooking.

Bacterial Toxins. By W. E. van Heyningen, M.A., M.Sc., Ph.D., senior research officer, Sir William Dunn School of Pathology, University of Oxford. 8°, cloth, 133 pp., with 14 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $3.50.

This monograph discusses the subject of bacterial toxins more fully than is usually done in textbooks of pathology, bacteriology and biochemistry. It presents the point of view of a biochemist and is based on a course of four public lectures given at University College, London, in the latter part of 1949. A bibliography of 21 pages is appended to the text. The excellent printing was done in Holland. There are indexes of subjects and authors. The monograph should be in all medical libraries.

A Pediatric Manual for Mothers: Questions and answers on the care and feeding of infants and children. By Harry R. Litchfield, M.D., consultant in pediatrics at Rockaway Beach Hospital, chairman and attending pediatrician at Beth-El Hospital, senior attending pediatrician at Brooklyn Women's Hospital and Brooklyn Thoracic Hospital and director of pediatrics at the East New York Dispensary, Brooklyn, New York; and Leon H. Dembo, M.D., director of pediatrics at St. Ann's Hospital, senior visitant in pediatrics at St. Luke's Hospital, physician-in-charge at St. Ann's Infant Home, consultant in pediatrics at Polyclinic Hospital and senior clinical instructor in pediatrics at the School of Medicine, Western Reserve University. 12°, cloth, 269 pp. New York: Grune and Stratton, 1951. $2.50.

This new type of popular book for mothers should prove easy to use because of its arrangement into major topics. There is a table of contents and a good index.

Perspectives in Human Malnutrition: A contribution to the biology of disease from a clinical and pathological study of chronic malnutrition and pellagra in the African. By Joseph Gillman, D. Sc., M.D., and Theodore Gillman, M.Sc., M.B., Departments of Physiology and Anatomy, Medical School, University of the Witwatersrand, joint nutrition unit of the Council of Scientific and Industrial Research and the University of the Witwatersrand, Johannesburg, South Africa. 4°, cloth, 584 pp., with 259 illustrations and 45 tables. New York: Grune and Stratton, 1951. $18.00.

This comprehensive treatise is well described by its title and should prove to be an essential reference work on malnutrition and pellagra. There is an extensive bibliography of 48 pages and indexes of authors and subjects; the publishing is excellent. The book should be in all medical libraries.

Introduction to Motherhood. By Grantly D. Read, M.A., M.D. (Cambridge). 12°, cloth, 104 pp., with 21 illustrations. New York: Harper and Brothers, 1951. $1.75.

This manual for the expectant mother is well written in simple language; it covers the period from the fertilization of the ovum to that of postnatal care for mother and child. The printing is well done, with legible type on a soft paper.

Poisons: Their isolation and identification. By Frank Bamfort, B.Sc. Third edition, revised by C. P. Stewart, D.Sc., Ph.D., reader in clinical chemistry, University of Edinburgh, and senior biochemist, Royal Infirmary, Edinburgh. With a foreword by Sir Sydney Smith, C.B.E., M.D., F.R.C.P., Regius Professor of Forensic Medicine, University of Edinburgh. 8°, cloth, 316 pp., with 23 illustrations. Philadelphia: The Blakiston Company, 1951. $5.50.

In this new edition of a standard manual the material has been brought up to date, the section on the barbiturates has been expanded and a short section has been added on the antihistaminic drugs. The printing was done in Great Britain; there is a good index. The book should prove valuable to toxicologists and others interested in poisons.

From a Doctor's Heart. By Eugene F. Snyder, M.D. With a foreword by Paul D. White, M.D. 8°, cloth, 251 pp., with 17 illustrations and frontispiece. New York: Philosophical Library, 1951. $3.75.

This book is the autobiography of a European refugee physician who came to the United States, narrowly escaped death from a coronary thrombosis and then proceeded to practice medicine to the present time. He established an office in Chicopee Falls, Massachusetts, in 1940, one year after arriving in this country. The story is written in the form of a discussion among Dr. Snyder, his wife, also a physician, and their teen-age son. It contains data comparing ways of life in Russia, Middle Europe and the United States. It also tells how to live with a damaged heart.

Primary Anatomy. By H. A. Cates, M.B., professor of anatomy and director of the School of Physical and Health Education, University of Toronto. Second edition. 4°, cloth, 344 pp., with 405 illustrations. Baltimore: The Williams and Wilkins Company, 1951. $6.00.

The first edition of this practical anatomy book was published in 1948. In this edition Dr. Cates has made a complete revision of the text and has added over one hundred new illustrations. There is a good index, and the type is excellent.

Review of Physiological Chemistry. By Harold A. Harper, Ph.D., professor of biology (biochemistry), University of San Francisco, lecturer in surgery, University of California School of Medicine, biochemist consultant to the Metabolic Research Facility, United States Naval Hospital, Oakland, and director, Biochemistry Laboratory, St. Mary's Hospital, San Francisco. Third edition. 4°, cloth, 260 pp., with illustrations. Palo Alto, California: University Medical Publishers, 1950. $3.50.

The first edition of this textbook was published in 1939. Much of the material has been drawn from the author's lectures and is intended as a supplement to the standard texts on biochemistry and as a companion volume to these texts.

Companionship of Water and Electrolytes in the Organization of Body Fluids. By James L. Gamble, M.D. 4°, paper, 90 pp., with 42 illustrations. Stanford, California: Stanford University Press, 1941. $2.50. (Lane Medical Lectures.)

The four lectures comprising this series are based on the work of the author, over a long period of years, on the physiology and pathology of body fluids. The publication of the Lane Lectures began in 1921; to date four complete volumes have been published. The set should be in the reference collections of large and regional medical libraries.

Manual Therapy. By James B. Mennell, M.A., M.D., consulting physician in physical medicine, St. Thomas's Hospital, London. 8°, cloth, 64 pp., with 10 illustrations. Springfield, Illinois: Charles C Thomas, 1951. $2.25. (Publication No. 85, American Lecture Series.)

This small monograph briefly discusses massage, assisted and passive movements and joint manipulation.

Atlas of Cross Section Anatomy of the Brain: Guide to the study of the morphology and fiber tracts of the human brain. (Fifth section of Emil Villiger's *Brain and Spinal Cord.*) Revised by Eugen Ludwig, professor of anatomy, University of Basel. With the *Atlas* further revised by A. T. Rasmussen, professor of anatomy, University of Minnesota. 4°, cloth, 63 pp., with 63 plates. New York: The Blakiston Company, 1951. $5.00.

This collection of Weigert sections of the brain, reproduced from the well known atlas of Dr. Villiger, provides a relatively inexpensive form of these excellent plates. To the Villiger series Dr. Rasmussen has added a number of carefully selected sagittal sections from the collection in the Department of Anatomy of the University of Minnesota. An index of over 10 pages concludes the book. It should be in all collections on the brain.

Gesundheitsfürsorge: Zeitschrift für die gesundheitlichen Aufgaben im Rahmen der Familienfürsorge. April, 1951. Vol. 1, No. 1. 4°, paper, 19 pp. Stuttgart: Georg Thieme, 1951. Subscription: DM 8.00.

This new periodical on health is edited by the German Central Committee for the Prevention of Tuberculosis, the German Union for the Health of Children and the Ministry of the Interior and Labor. It is published monthly.

Chronology of Ophthalmic Development: An outline summary of the anatomical and functional development of the visual mechanism before and after birth. By Arthur H. Keeney, M.D., Wills Eye Hospital, Philadelphia. 4°, paper, 22 pp. Springfield, Illinois: Charles C Thomas, 1951. $2.00. (Publication No. 99, American Lecture Series.)

Ophthalmic development is portrayed in three large chronologic charts, from the first to the tenth week of prenatal life and in the postpartum period from the neonatal to the eleventh year of life, puberty, adolescence and the ages of twenty to twenty-five years. The monograph is concluded with a table of the functional development of vision and binocularity, from the third fetal month to nine years.

NOTICES

THE CHILDREN'S MEDICAL CENTER

Dr. Alfred Gellhorn, Director of the Cancer Research Institute and associate professor of medicine, Columbia University College of Physicians and Surgeons, will speak on "Neoplastic Disease and Internal Medicine: a 'New' Look," at the Auditorium of the Jimmy Fund Building, Children's Cancer Research Foundation, 35 Binney Street, Boston, on February 27, at 12:00 m. Members of the medical profession are invited to attend.

PEDIATRIC SEMINAR

The Department of Pediatrics of Massachusetts General Hospital will present a panel discussion on chronic and recurrent infections in children at 7:15 p.m. on February 20 in the White 3A Amphitheatre of the hospital.

AMERICAN PSYCHIATRIC ASSOCIATION

The American Psychiatric Association will present a New England regional research conference on February 28 and 29 at the Boston Medical Library, 8 Fenway, Boston.

The meetings will be open to all persons interested in psychiatry and related fields — especially research workers. Morning sessions will be held from 9:30 a.m. to 12:30 p.m., the afternoon sessions from 2:30 to 5:30 p.m. Papers covering a variety of topics will be presented on Thursday evening at 8:15 p.m. Speakers of national prominence will be heard. The programs will be concerned with work in progress as well as completed research.

Further information may be obtained from Dr. Max Rinkel, 479 Commonwealth Avenue, Boston.

AMERICAN COLLEGE OF CHEST PHYSICIANS

The Eighteenth Annual Meeting of the American College of Chest Physicians will be held at the Congress Hotel, Chicago, Illinois, June 5–8.

The Board of Examiners of the College announces that the next oral and written examinations for fellowship will be held in Chicago on June 5. Candidates for fellowship who wish to take the examinations may write to the Executive Secretary, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

COLLEGE OF MEDICAL EVANGELISTS

The Postgraduate Assembly and Convention sponsored by the Alumni Association of the College of Medical Evangelists School of Medicine will be held at the Biltmore Hotel, Los Angeles, March 2–4.

Information may be obtained from Evelyn R. Strachan, Managing Director, 312 North Boyle Avenue, Los Angeles 33, California.

SOCIETY MEETINGS AND CONFERENCES

FEBRUARY 16–27. Springfield Hospital. Page 204, issue of January 31.

FEBRUARY 19–26. Boston City Hospital House Officers' Association Page 160, issue of January 24.

FEBRUARY 20–MARCH 26. Lahey Clinic Fellowship Teaching Program. Page 160, issue of January 24.

FEBRUARY 18 AND 19. American College of Surgeons. Page 203, issue of January 31.

FEBRUARY 19. South End Medical Club. Page 242, issue of February 7.

FEBRUARY 20. Pediatric Seminar. Notice above.

FEBRUARY 25 AND APRIL 15. Massachusetts Society for Research in Psychiatry. Page 792, issue of November 15.

FEBRUARY 26, MARCH 25 AND APRIL 24. Norfolk District Medical Society. Page 710, issue of November 1.

FEBRUARY 27. Children's Medical Center. Notice above.

FEBRUARY 28 AND 29. American Psychiatric Association. Notice above.

MARCH 1, APRIL 5 AND MAY 3. New England Society of Anesthesiologists. Post-Graduate Education Course. Page 966, issue of December 20.

MARCH 2–4. College of Medical Evangelists. Notice above.

MARCH 3–5. National Cancer Conference. Page 242, issue of February 7.

MARCH 3–APRIL 30. Seventh Postgraduate Lecture Course. Page 274.

MARCH 10–13. New Orleans Graduate Medical Assembly. Page 956, issue of December 13.

MARCH 12. Northeastern New York Radiological Society. University Club, Albany, New York.

MARCH 13. Sinusitis. Dr. Francis L. Weille. Pentucket Association of Physicians, 8:30 p.m. Haverhill.

MARCH 24–28. American College of Chest Physicians. Page 160, issue of January 24.

MARCH 31–APRIL 4. Fifth American Congress on Obstetrics and Gynecology. Page 832, issue of November 22.

APRIL 21–25. Cancer Seminar. Page 114, issue of January 17.

APRIL 23. Massachusetts Academy of General Practice. Springfield.

APRIL 23. New England Obstetrical and Gynecological Society (Spring Meeting). Hartford, Connecticut.

MAY 1–3. American Goiter Association. St. Louis, Missouri.

MAY 20–22. Massachusetts Medical Society. Hotel Statler, Boston.

MAY 26–29. National Tuberculosis Association. Copley Plaza and Statler hotels, Boston.

JUNE 5–8. American College of Chest Physicians. Notice above.

JUNE 18–20. Massachusetts Public Health Conference. Amherst.

JULY. Commonwealth and Empire Health and Tuberculosis Conference. Page 792, issue of November 15.

JULY 7–12. International Diabetes Federation. Page 997, issue of December 20.

JULY 8–11. Thirteenth British Congress of Obstetrics and Gynaecology. Page 916, issue of December 6.

JULY 14–19. International Congress of Physical Medicine. Page 998, issue of June 28.

SEPTEMBER 7–9. Combined session of the New Hampshire and Vermont State Medical Societies, Mount Washington Hotel, Bretton Woods, New Hampshire.

OCTOBER 29. New England Obstetrical and Gynecological Society. Annual Meeting. Hotel Somerset, Boston.

DISTRICT MEDICAL SOCIETIES

HAMPSHIRE

MARCH 5. Cooley-Dickinson Hospital, Northampton.

MAY 7. Annual Meeting. Jones Library, Amherst.

MIDDLESEX SOUTH

APRIL 30. Hotel Continental, Cambridge.

NORFOLK

FEBRUARY 26. Boston Medical Library.

MARCH 25. Boston Medical Library.

APRIL 22. Boston Medical Library.

MAY 7. Place to be announced.

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, FEBRUARY 21

THURSDAY, FEBRUARY 21

*9:00–10:00 a.m. Grand Rounds. Robert Breck Brigham Hospital.

12:00 m.–1:00 p.m. Chronic Ulcerative Colitis. Dr. Leland S. McKittrick. New England Center Hospital, Stearns Auditorium.

*4:00–5:00 p.m. Medical Division Lecture. Mount Auburn Hospital, Cambridge.

*4:30 p.m. Metal-Organic Complexes and Their Relations to Metal-Protein Specificity. Dr. Jack Schubert. Seminar under Auspices of University Laboratory of Physical Chemistry. Harvard Hall, Room 1.

5:00 p.m. Case presentation and pathological discussion followed by a subject of special presentation. Joslin Amphitheatre, New England Deaconess Hospital.

7:00 p.m. Medical Genetics. Dr. L. H. Snyder. Boston City Hospital.

SATURDAY, FEBRUARY 23

*11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

(Notices concluded on page xvii)